INTRATHECAL PHENOL TO RELIEVE SPASTICITY IN PARAPLEGIA

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IF a patient has the misfortune to be paralysed in the legs, it is usually better for the limbs to be flaccid rather than spastic. Spastic paralysis may be changed to flaccid paralysis by dividing the anterior spinal roots, which prevents impulses from getting through to the muscles, so they can no longer contract. The experience gained and the technique used in treating spasticity of the lower limbs by the intrathecal injection of solutions designed to destroy the anterior spinal roots are reported here. It must be stressed at the outset that this method of treatment must be used only when paraplegia is complete and there is no possibility of recovery from the paralysis.

The misery associated with total paralysis of the lower limbs may be aggravated by spasticity and its accompaniments. Besides the constant spasticity, there may be spasms coming on every few minutes or half-hour; they may be brought on by any sudden noise, by jarring of the bed, or by any attempt to move, whether carried out by the patient or by others. Though more common in the lower limbs, these spasms may involve the muscles of the back and abdominal wall. Both the spasticity and the spasms may be accompanied by pain. The pain of spasticity consists usually of a never-ceasing tiring ache, situated wherever the region of the spastic musculature is; thus it may be in the lower limbs, in the back, in the abdominal wall. Often a more severe pain accompanies the violent flexor, adductor, or extensor spasms—a pain so severe that the patient cries out with each spasm, and lies apprehensively awaiting the next spasm of agony. These patients may also suffer from a tiring feeling of muscular tension: they may feel as though the abdomen is in a constricting band or as though the back is like a board, and they may get a tearing aching feeling at the insertion of the spastic muscles. These feelings being almost continuous, the patient becomes tired out. As each spasm may be accompanied by involuntary emptying of the bladder, the patient is often in a wet bed and increasingly liable to bedsores. There may be so much spasm of the adductors of the thighs that in some women it is very hard to insert a catheter.

It is easy to see, therefore, why it is better to have the lower limbs flaccid rather than spastic. If spasticity and spasms are removed, nursing is easier, and the patient can be moved more often. He is more willing to move himself, provided he retains the use of his arms, for the movements no longer provoke a spasm. Although the bladder in these patients is usually not under conscious control and empties automatically, it no longer tends to empty with every spasm; in the absence of spasms it can be trained to empty automatically at convenient periods, or, if a catheter life is preferable, this can be managed more satisfactorily. Further, bedsores, which were prevented from healing by the spasms, slowly heal. When spasticity has been relieved, deformities may be slowly corrected, either by gentle traction and physiotherapy, or by placing the limb in some form of plaster and very gradually correcting the deformity by slow extension or flexion. Again, it is only after spasticity and spasms have been removed that physiotherapy may become really useful.

The spasticity which results from overactivity of muscles can be relieved by cutting all the anterior spinal roots supplying the muscles concerned; this division of roots is a large and difficult operation and would have to be undertaken in patients who are usually in not very good health. An alternative would be to destroy these roots by means of a chemical substance. The technique described here consists of the intrathecal injection of a concentrated lipid solution of phenol designed to destroy the anterior spinal roots supplying the muscles causing most of the trouble in the spastic state.

Chemical Anterior Rhizotomy

The first use of intrathecal phenol in lipid solution was reported by Maher (1955). He used a solution of phenol in glycerol to relieve the severe pain of cancer. In 1957 he recorded a further series of patients treated by this solution and by phenol dissolved in ' Myodil ', including some patients whose pain was not due to cancer. Maher's method was to inject intrathecally a 5% solution of phenol so that the phenol should destroy the nerve fibres or the ganglia concerned in the transmission of impulses giving rise to pain.

To destroy the anterior roots permanently, the most useful solvents for phenol have been found to be myodil (ethyl iodophenylyndecylate) and glycerol. Various concentrations of phenol in these solvents have been used, and experiments in cats have been undertaken; the results of these will be published later with T. A. Sears and M. C. Smith.

The best solution for permanent destruction of all fibres of the anterior roots has been found to be phenol in glycerol. A suitable concentration is 20%, but a 10% solution has sometimes been adequate. A solution of phenol in myodil is also satisfactory; at equivalent concentrations the action of this solution is weaker; it seems that a 25% solution is necessary to destroy all anterior root fibres. The amount of the solution is determined by the number of roots it is designed to affect; although this is so, the variability in the number of roots affected is large. Usually 1 ml. affects 7–8 roots, 0·75 ml. affects 4–6 roots, and 0·5 ml. affects 2–3 roots. Yet in one patient 0·5 ml. of the 20% solution of phenol in glycerol affected 7 roots, and in another patient 0·75 ml. of this solution affected only 3 roots. With phenol in myodil, in one patient 1 ml. of the 20% solution affected 8 roots while in another patient 1·5 ml. affected only 5 roots.

It might be thought that such strong solutions of phenol must be harmful, but no untoward reactions, such as meningitis or phenol poisoning, have yet been encountered when the roots of the lower limbs are being treated. Changes in the constituents of the cerebrospinal fluid have been insignificant—for example, the largest amount of the strongest solution used (2 ml. of 20% phenol in glycerol) was associated with a rise of protein to 60 mg. per 100 ml. without any increase in cells.

Advantages

The advantages over surgery of a method taking half an hour and not upsetting the patient are obvious. Phenol in lipid solution has the following advantages. It has a higher specific gravity than C.S.F. and it is thus easy to direct its flow around the correct roots. It is relatively easy to manage since it is rather viscid. With lipid solutions of phenol the first anæsthetising effect is transitory; if during this early period the solution is caused to run off a root, minimal or no damage to this root will occur. Phenol in lipid solution first blocks conduction in nerve fibres, and later destroys the fibres, provided it is left surrounding the roots for long enough. This means that the sensory and motor deficit resulting from the effect of the phenol solution on the posterior and anterior roots may be easily determined, allowing ample time to alter the position and slope of the patient if this is necessary. As destruction of nerve fibres is preceded by blocking of conduction in them these injections may be given without pain. The effects may not be complete on all roots—for instance, it may be found that there is dense loss of all forms of sensibility in the 5th lumbar dermatome, moderate loss in the 4th lumbar and 1st sacral dermatomes, and slight loss in the 3rd lumbar and other sacral dermatomes.

Disadvantages

One of the disadvantages is that the nerves supplying the sphincters of the bladder and rectum may be destroyed. If the aim is to destroy the 1st, 2nd, and 3rd anterior lumbar roots so as to prevent flexion of the lower limb on the pelvis by denervating the psoas muscle, and/or to destroy the 3rd and 4th anterior lumbar roots to prevent adduction, the danger of destroying also the 2nd, 3rd, and 4th sacral roots, which supply the sphincter musculature, is not great. But if the object is to destroy the nerve supply of the hamstrings, the 5th lumbar, 1st, and 2nd sacral roots, then there is considerable danger of paralysing the sphincters. To do this completely is a disaster, especially in women, since there is no satisfactory wearable urinal for women.

Apart from the danger of destroying certain anterior roots that should be left intact, a further objection to the method is that some posterior root fibres are inevitably involved: the injection causes a degree of loss of sensibility and even anæsthesia in the dermatomes of the treated roots. This renders the patient liable to injury of the analgesic skin, and it may contribute in part to the development of bed-sores, the more so as the previously lying patient may now prefer to spend long periods sitting in a chair. Pressure sores are just as likely to develop when the patient constantly sits in one position as when he lies in bed in one position. More common than anæsthesia is a positive sensation of numbness; this is more likely to occur where the loss of sensibility is not dense. This subjective sensation, however, is regarded by most of these patients as a cheap price to pay for the riddance of spacticity, spasms, and pain.

Method

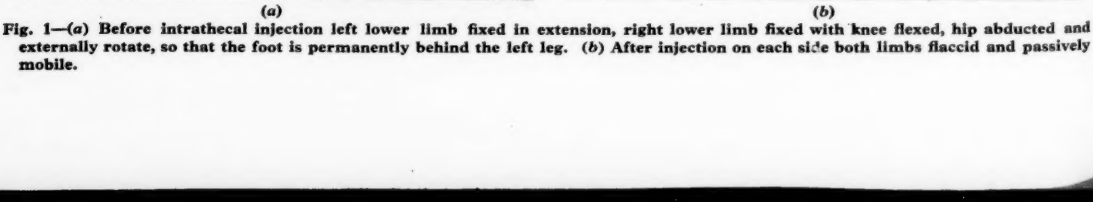
It is best to carry out the procedure with radiological control, for it is advisable to know with certainty in which space the lumbar puncture needle has been introduced; with these patients, who may have severe and fixed deformities of the spine, the usual landmarks—never a reliable guide—may be misleading. The availability of an easily manipulated tilting table is also invaluable.

The patient is placed in the usual lateral position for a lumbar puncture, with the side to be treated lowermost. Then by means of the tilting table and the use of hard cushions the spine is so positioned that the roots to be treated are at the lowest point. The patient must also be in a suitable position for taking a lateral film of the vertebral column. At this time or later, after the needle has been put in, the patient is turned a few degrees anteriorly, so that the back makes an angle of about 75–80° with the table. The needle is inserted at the space corresponding to the exit foramen of the most important root to be treated. After the needle has been inserted in the correct space, final attention is given to the position and slope of the patient.

The needle is then turned so that its bevel is directed on to the subjacent roots, thus permitting the injected fluid to flow on to these roots in their intervertebral foramina. When an entirely unilateral effect is needed, it is best to use Sheldon's vertebral needle. 0·5 ml. of the solution is injected, over the period of a minute. Provided the patient has good sensibility, he usually reports in about 40 seconds a sensation of warmth or warm tingling running down the leg on which he is lying or down both legs, or, if he usually has pain, he will report that his pain has gone.

From now onwards, the tilting and positioning of the patient is monitored by the distribution of the anæsthesia and analgesia and of the various muscle groups rendered flaccid and the loss of deep reflexes. It may be necessary to inject a further 0·25 ml. to obtain complete relief. The patient is left lying in the same position in order to keep the solution in contact with the nerve roots for 30 minutes. He may then be moved, because no further effects from the phenol are to be expected.

Later in the day the patient may be allowed up but should return to bed if he complains of a headache. The routine is



(*a*) (*b*)

Fig. 1—(*a*) Before intrathecal injection left lower limb fixed in extension, right lower limb fixed with knee flexed, hip abducted and externally rotate, so that the foot is permanently behind the left leg. (*b*) After injection on each side both limbs flaccid and passively mobile.

(a) (b)

Fig. 2—(a) Before intrathecal injection lower limbs fixed in position shown; left foot could not be moved from behind right knee. (b) After injection on each side, lower limbs completely flaccid, and can be placed passively in abduction.

the same as that used after a myelogram: the essential precaution is to prevent the patient lying quite flat, so as to avoid any possibility of the solution running into the head. In the period soon after the injection the patient's ability to micturate is inquired after and appropriate measures taken should it be disturbed.

Results

In 25 patients so treated, the diagnoses were: disseminated sclerosis (18), amyotrophic lateral sclerosis (2), sequelæ of nerofibroma compressing the cord (1), irradiation necrosis of the cord (1), collapse of vertebræ on to the cord (1), intramedullary tumour (1), and congenital diplegia (1). So far no cases of spasticity affecting the upper limbs have been treated. The results have been most satisfactory.

For instance, a patient who had been bedridden for 5 years and who, every time she moved, suffered great pain due to spasms of her legs, is now able to spend the entire day up in a wheeled chair and is free from pain. The original position of her lower limbs, one flexed and one extended, is shown in fig. 1a and the position of the flaccid legs after injection in fig. 1b.

Another patient who had been completely bedridden had had both lower limbs fixed in extension; this position was accompanied by most painful extensor spasms every 10 minutes. After the injection, she is free from pain and is up in a wheel-chair all the time; she is able to go out in her chair, and to earn money at home addressing envelopes, an impossibility before treatment.

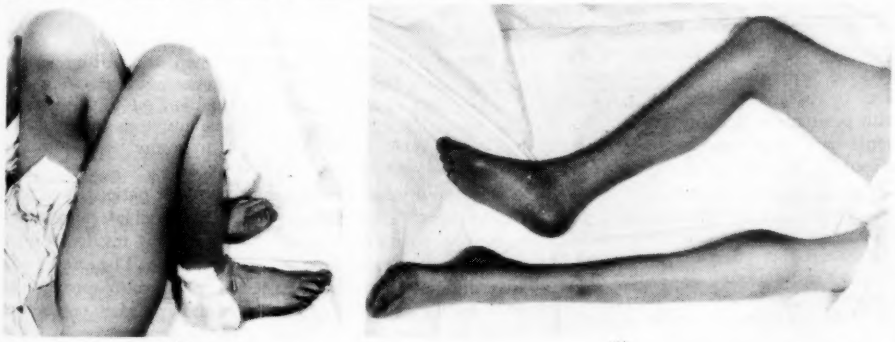
A patient whose only enjoyments left in life were photography and sketching had had to give them up, for as soon as he got his camera on a tripod or fixed up his easel, a strong flexor spasm of his lower limbs caused him to fall to the ground, knocking over all his apparatus. After treatment he has been able to pursue these hobbies again, being free from spasms and pain.

Before injection another patient's lower limbs were rigidly held in the position shown in fig. 2a; they were so firmly adducted that the legs were developing pressure sores. After the injection they are shown (fig. 2b) in maximal abduction, a position that can now be maintained owing to loss of spasticity.

Fig. 3a shows the legs of another patient firmly and painfully fixed in flexion and adduction; and fig. 3b shows them immediately after the injection. Eventually physiotherapy corrected the position of the legs so that they could be fully extended.

The immense difference the removal of pain, spasticity, and spasms has made to the lives of these severely incapacitated patients has been striking; their lives become not only bearable but enjoyable. With the lower limbs made flaccid they are able to be up in easy chairs and go out in wheel-chairs and cars and go to concerts and cinemas.

It has been very interesting to observe in some patients with disseminated sclerosis, who were injected because no voluntary movement was possible and who had very great spasticity, an unmasking of some voluntary movement in muscle groups other than those affected by the injection. Although the range and power of these movements have been too slight to be of use, this return of some voluntary movement demonstrated how such movements may be prevented by spasticity. It has drawn attention to the possibility of increasing such movements in patients who are less paralysed and who have spasticity in the legs. Modifications in the technique described here are still being investigated, in the hope of evolving a treatment for



(a) (b)

Fig. 3—(a) Before intrathecal injection both lower limbs fixed in flexion and adduction. (b) After injection on each side, both lower limbs flaccid. Flexion contraction of right knee later removed by physiotherapy. Note healing of bedsore on right heel, and subsidence of oedema.

forms of paresis where the spasticity interferes with the ability to walk and move, when these are still present.

Regeneration of fibres of the anterior roots after these injections is certainly possible, for there has been no gross displacement of nerve fibres and no macroscopic disturbance of intraneural plexi. Spasticity and spasms have recurred, possibly because of regeneration; but in only 1 of 25 patients treated by injection has a return of spasms been severe enough to warrant another injection a year after the first; a year after the second injection spasticity had not returned. There seems to be no reason why the injection should not be repeated for recurrences even more frequently than once a year.

Summary

A method of destroying the anterior spinal roots painlessly is described. This has been performed to render flaccid the spastic lower limbs of subjects suffering severe pain associated with extreme spasticity and spasms. The technique consists of the introduction into the spinal canal of phenol in concentrated solution in glycerol or myodil, so that it surrounds the anterior nerve roots for half an hour.

I should like to thank the physicians of the National Hospital, Queen Square, London, for referring patients to me for the investigation on which this report is based; and Dr. E. Arnold Carmichael for the facilities and encouragement he gave me.

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INTRATHECAL PHENOL IN THE TREATMENT OF REFLEX SPASMS AND SPASTICITY

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REFLEX peripheral spasms are a common complication of spinal and cerebral lesions. They first develop in the feet and legs and are excessive self-propagating maximal motor responses to a minimal noxious sensory stimulus. These spasms are very disturbing to the patient, for they are often very painful, prevent sleep, and may be so violent as to project a sitting patient on to the floor. They may also be associated with involuntary defæcation and urination. The spasms may be flexor, extensor, or any combination of the two. If untreated the limbs become fixed in either flexion or extension and contractures eventually develop, with permanent deformity.

A variety of treatments have been used in the past, but most of these have serious drawbacks:

Anterior rhizotomy.—This is effective in abolishing spasms, but causes a complete loss of voluntary movement as well. This treatment is obviously contraindicated in ambulant patients, and severely disabled paraplegics are often too debilitated to stand the operation, which is a major procedure. Munro (1952) described a small series of patients treated operatively with anterior rootlet rhizotomy. In this some voluntary movement was retained but the second criticism still applies.

Intrathecal solutions.—The use of alcohol (Cooper and Hoen 1949, Sheldon and Bors 1948, Stellar 1953) again proved effective, but led to loss of voluntary movement and of sensation, although most of the cases described had very little useful function left before treatment. Berlin (1954) reported the treatment of 6 male paraplegics with intrathecal mephenesin. Here again undesirable side-effects, such as loss of motor power, sensation and bladder control, occurred, and repeated intrathecal injections were required.

Drugs.—Many have been tried and proved very disappointing. Curare, mephenesin, chlorpromazine, zoxazolamine, meprobamate, and, more recently, 'Coltromyl' (thiocolchicoside), have all been tried. Separately or in combination they are effective in some cases, but often they afford no relief at all or produce disabling side-effects such as gastrointestinal upsets, drowsiness, and generalised weakness.

Sciatic-nerve injection.—Munro and Spatz (1959) reported the successful treatment of one case of reflex spasms in the legs with multiple injections of 1% procaine to the sciatic nerves.

Intrathecal phenol was first employed by Suvansa (1931) in the treatment of tetanus, using a 1/400 aqueous solution. More recently there have been a number of reports of the use of intrathecal phenol dissolved in glycerin or 'Myodil' in the treatment of intractable pain (Maher 1955, 1957, Brown 1958, Nathan and Scott 1958). Relief of pain has been produced with very little if any neurological deficit. Transitory and sometimes permanent loss of reflexes and tone was mentioned as an occasional complication and the successful treatment of a very few patients with reflex spasms was also reported. It thus seemed to us to be worth while treating a larger series by this method.

32 patients have so far been treated: all had severe spasticity of one or both legs and 25 disturbing and painful reflex spasms. 24 were female and 8 male. The youngest treated was 2 years and the oldest 75. All were paraplegic except 1 patient with hemiplegia due to cerebral hæmorrhage. The diagnoses were:

Disseminated sclerosis	20	Congenital paraplegia	1
Extradural abscess	2	Devic's disease	1
Arteriosclerotic quadriplegia	1	Neurofibroma of nerve root	1
Cerebral hæmorrhage	1	Secondary carcinoma	1
Cervical cord radiation damage	1	Syringomyelia	1
Cervical spondylosis	1	Tuberculous meningitis	1

Materials and Method

Phenol was used in every case, either in myodil or glycerin. 36 injections of each have been given and 5 patients have had both.

Phenol in myodil.—Dry crystals of phenol are dissolved in myodil immediately before use, varying strengths being used between 5% and 20%. The solution is injected in amounts varying between 1·5 ml. and 3 ml. Myodil is radio-opaque and initially injections were carried out under fluoroscopic control. Later this procedure was found to be unnecessary. The column of phenol in myodil tends to pool around the site of injection and does not move significantly unless there is at least 10° of tilt.

Phenol in glycerin.—This solution is prepared by dissolving dry phenol crystals in glycerin. It is then sterilised by heating to 160°C in a hot-air oven and is stored in sterile ampoules. It is used in a strength of 5% and from 1–2 ml. of this is used. This solution is more effective in relieving spasms and spasticity but is also more liable to give rise to complications such as sensory loss and bladder disturbances.

Both solutions are hyperbaric, so the patient is placed on the side to be treated, in the conventional lateral lumbar-puncture position. Careful positioning is needed with a slight downward slope of the spine. The needle is inserted between L2 and L3. When cerebrospinal fluid appears the needle is advanced a further 1 mm. to prevent subdural injection. 0·5 ml. of the appropriate solution is then injected. When glycerin is used a sensation of warmth is felt in the lowermost leg in the cutaneous distribution of the roots affected. This is not unpleasant and

wears off after about 15 minutes. The myodil solution often produces the same sensation, or sometimes pins and needles. If, with this initial injection, the paræsthesiæ are felt in the buttocks the solution is too low and there is an increased likelihood of bladder disturbance. The procedure should then be temporarily abandoned and repeated later in a higher space. If the paræsthesiæ are felt in the region of the knee and thigh the rest of the injection is then given. After this the patient is kept in the same position for 30 minutes. If there is a bloodstained tap or nerve-roots are hit on the way in, injection should be deferred. If the roots are damaged the effects of the phenol are greatly enhanced.

The number of injections needed varied from 1 to 6.

No. of injections	*No. of cases*	*No. of injections*	*No. of cases*
1	10	4	4
2	13	6	2
3	4		

Complications

Headache.—Only 2 patients had headache after injection. This was moderately severe and was associated with neck stiffness. In both cases it cleared after 24 hours.

Bladder disturbance occurred in 6 cases. In 2 there was transitory retention that required catheterisation on one occasion, and in 2 others there was incontinence lasting 24 hours. The remaining 2 had more serious disturbances; 1 was incontinent for several weeks and the other has had no bladder control since the injection six months ago. Both the last 2 patients have disseminated sclerosis and were frequently incontinent before injection. This complication occurred only when glycerin was used as the solvent.

Pain in the leg occurred in 3 cases and had the character of a radiculitis. It cleared completely in a few days.

Sensory loss.—Transient numbness of the leg lasting several hours affected many patients, but in only 9 was it permanent. All these had some sensory disturbance before treatment and were made worse in this respect. All these patients, however, were bedridden and none was incapacitated by it.

Sensitivity reaction.—About 15 minutes after injection with the myodil solution 2 patients had quite severe reactions. These consisted of a drop in blood-pressure, sweating, increase in pulse-rate, shivering, and angor animi. Both recovered rapidly after an antihistamine injection and were none the worse for the experience. Both these patients had had a previous injection.

2 patients in this series have died, but neither death was attributable to the injections (both had carcinomatosis and 1 also had a quadriplegia following radiation damage to the cervical cord).

Results

The results of the treatment of spasticity and reflex spasms are difficult to assess. So far, no objective means of measuring spasticity have been found and clinical observation remains the best method. Range of movement measurements are inaccurate and electromyograph records show much daily variation. The degree of spasticity frequently alters from day to day and, as Kuhn and Bickers (1948) pointed out, suggestibility plays a very important part in invalidating results.

In this study, 30 out of the 32 patients had had a paraplegia for several years and the other 2 had rapidly worsening reflex spasms of a few weeks' duration.

CLINICAL ASSESSMENT OF SPASTIC PATIENTS AFTER TREATMENT

No. of cases	Much improved	Improved	No change	Made worse
32	11	15	5	1

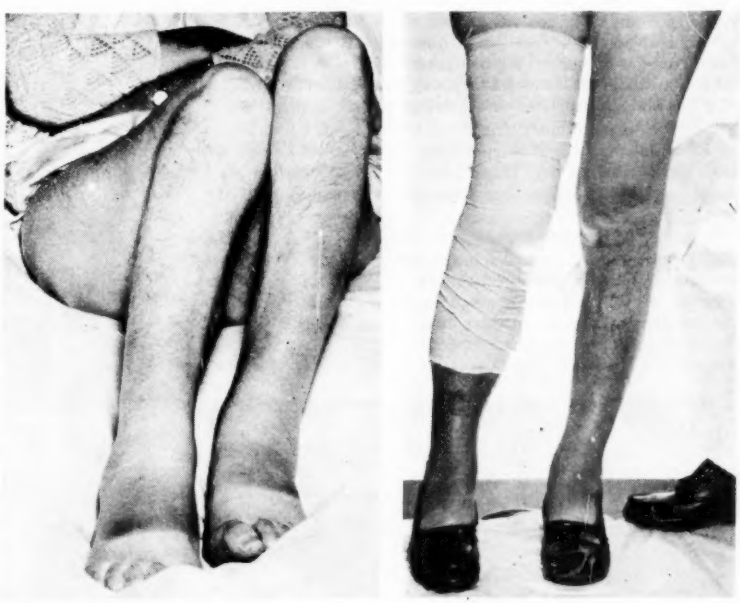
Much improved: Great reduction in tone. Unmasking of voluntary movement. Ability to straighten legs. Improvement in gait.
Improved: Moderate reduction in tone. Easing of nursing problems. Healing of intractable bed-sores. Greater comfort.
No change: Tone unaltered.
Made worse: Loss of bladder function.

Reflex Spasms

25 patients had severe spasms. All had previously been treated with adequate doses of one or more relaxant drugs with little relief. The spasms were almost always worse at night, interfering with sleep, and in 14 patients they were very painful. They were so violent in 5 patients that they were thrown out of chairs and off bedpans. In one girl of 19 the spasms spread to the anterior abdominal wall and caused frequent vomiting.

In 16 cases the spasms were abolished and in 7 others were much reduced and became painless. The 2 remaining patients, both with carcinomatosis and severe spasms, died within a few days of the injections and it was impossible to assess the results. So far the longest period of follow-up has been 10 months without relapse. 4 patients have had a recurrence of less severe spasms and have all responded to reinjection.

In addition to greater comfort and improved sleep other benefits resulted. 5 patients were enabled to sit out of bed in chairs and in 2 of these troublesome bedsores have healed. Previously these patients were unable to lie prone on account of the spasms. In 2 cases urgency of micturition with occasional incontinence has been improved. 1 patient showed remarkable psychological improvement after treatment; she had had painful spasms for many months and from being depressed, irritable, and surly she became cheerful and cooperative.



(*a*) (*b*)

Fig. 1—Case 1 (*a*) before and (*b*) after treatment.

Spasticity

All the patients treated had spastic legs. 26 showed considerable reduction of tone assessed clinically, and this was maximal within an hour or so of injection. Tone gradually returned after several weeks, but not to the previous level. In 3 cases the treated leg became completely flaccid and useless within a few minutes of the injection. This gave rise to some anxiety as all these patients had previously been able to stand. After 12–24 hours, however, sufficient tone and power returned to enable all of them to stand again. In all 3 spasms were abolished. In 5 cases there was no improvement. All these had had paraplegia-in-flexion with contractures for many years. Reduction in tone has made nursing care in many of these patients much easier and has increased their comfort. The results are summarised in the accompanying table.

In 2 patients, abolition of flexion deformity has enabled them to stand and take a few steps.

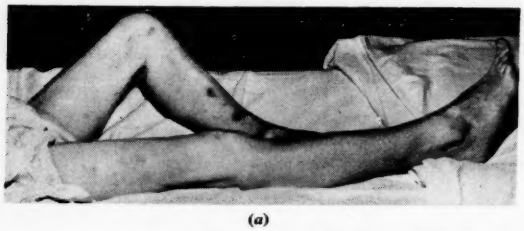
Case 1.—A woman of 46 with a paraplegia, progressing since 1946. She had not walked for 3 years and for the past 18 months has not stood and has had difficulty in sitting in a chair on account of severe flexor and extensor spasms. Both legs were grossly spastic, the right more than the left, with marked flexion and adduction (fig. 1a). They could be straightened with difficulty but immediately took up their former position when released. Voluntary movement was present but every attempt induced a flexor spasm. There was some posterior-column sensory loss.

One injection of 3 ml. of 10% phenol in myodil was given in the right lateral position. After this there was a great reduction of tone and the spasms were abolished. The patient was able voluntarily to straighten both legs, and to stand with the aid of one person (fig. 1b). Considerable voluntary movement masked by the spasticity has reappeared and there is no additional sensory loss. She has had occasional incontinence for years and there was no deterioration of bladder function after treatment. At present, three months after treatment, there has been no relapse and the patient is taking a few steps between parallel bars.

Case 2.—A woman of 53 with disseminated sclerosis. She has had a paraplegia since 1939, slowly getting worse. She has had flexor and extensor spasms for many years, much more severe and painful in the past 9 months. In the few weeks before admission her left leg had gone into flexion and she was unable to straighten it herself. Walking had become impossible. She has had urgency and occasional incontinence for years.

She had bilateral spasticity of the legs, the left being flexed to 30° and the right held extended (fig. 2a). She was able to lift both legs against gravity. Her left leg could not be straightened because of pain. There was some posterior-column sensory loss.

3 ml. of 10% phenol in myodil was injected in the left lateral position. This enabled her to straighten the left leg, but spasms persisted. The injection was repeated and a similar amount of a $7^1/_2$% solution given on the right. There was no further sensory loss, no bladder disturbance, and she can now walk the length of the ward with elbow crutches. Occasional spasms still occur, but they are less severe and are painless. She still has slight difficulty in getting her left heel flat on the ground (fig. 2b).



(*a*) (*b*)

Fig. 2—Case 2 (*a*) before and (*b*) after treatment.

Discussion

The mechanism involved in the production of spasticity and reflex spasms is still not understood. Dogliotti (1931) first treated pain with intrathecal alcohol. Since that time many workers have confirmed that both alcohol and phenol can abolish pain without producing any detectable neurological deficit. Experience with our series so far indicates that spasms can be stopped and spasticity reduced in the same way. Further work is in progress in an attempt to elucidate this problem.

The effects of the solutions used vary a good deal from patient to patient. The 5% glycerin solution is more effective but is liable to give rise to sensory loss and weakness. Its use should be restricted to bedridden patients in whom these complications are not so important. The myodil solution is a perfectly safe treatment for patients who are able to walk a little and on several occasions has improved their gait by reducing spasticity. It is not so effective when spasms are very severe. Bladder complications have not proved a serious problem, although it is important to keep the solutions away from the lower sacral nerve-roots. Longer follow-up is needed in our cases. Experience so far suggests that relapse tends to follow after several months in some cases, but responds to further treatment.

The safety of the method has already been proved by our own experience and that of others in its use in cases of intractable pain. The object of this trial was to test its effectiveness in the treatment of reflex spasms and spasticity. It is clear that spasms can be abolished or greatly reduced without adding to the patient's disability.

Spasticity of varying severity has been treated. Long-standing severe paraplegics with contractures cannot be helped much unless they are troubled by spasms; but spasticity of lesser degree can be reduced, adding to the patient's comfort, enabling bedsores to heal, and simplifying nursing care. Many patients are incapacitated by the increase in tone rather than by weakness, and in some a surprising amount of voluntary power has been unmasked by its reduction. A few ambulant patients have been treated with success and an increase in mobility has resulted. A slow, scissors progression has been converted into a more rapid, wider-based gait.

Our aim is to treat a larger number of ambulant patients now that the safety of the treatment has been established. In these patients drugs have proved disappointing and surgery has no place.

Summary

Phenol dissolved in myodil or glycerin has been injected intrathecally in the treatment of 32 cases of reflex spasms and spasticity. The treatment is easy to perform and is not distressing to the patient. It is very effective in the

treatment of spasms: spasticity can be reduced and in some improved. The treatment is least effective in longstanding paraplegics with contractures.

Complications have not proved a serious drawback although the glycerin solution may produce weakness and some sensory loss. It should be used only for bedridden patients.

We wish to thank the following colleagues who were kind enough to refer patients to us: Dr. J. St. C. Elkington, Sir Russell Brain, Dr. J. B. Harman, Dr. Redvers Ironside, Dr. Evan Jones, Dr. V. Kendal, Mr. V. C. Snell, and Dr. H. de Wardener.

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ABSORPTION AND EXCRETION STUDIES OF THE POTASSIUM SALT OF 6 (α-PHENOXYPROPIONAMIDO) PENICILLANIC ACID *

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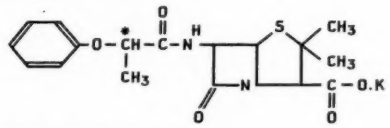
THE isolation and characterisation of 6-amino-penicillanic acid (Batchelor et al. 1959) has provided an approach for the synthesis of new penicillins. This paper describes the results obtained from the oral administration of a new synthetic penicillin, the potassium salt of 6 (*a*-phenoxypropionamido) penicillanic acid (BRL152), from comparative studies with the potassium salt of penicillin V (phenoxymethylpenicillin), and from preliminary studies with the sodium salt of penicillin G (benzyl penicillin) by intramuscular injection.

Chemistry

The structural formula of the potassium salt of 6 (*a*-phenoxypropionamido) penicillanic acid may be represented as follows:



Molecular formula: $C_{17}H_{19}KN_2O_5S$
Molecular weight: 402·51

BRL152 is the *N*-acylation product of 6-amino penicillanic acid (6-A.P.A.) and *a*-phenoxypropionic acid (the phenylether of lactic acid).

It is freely soluble in water and resistant to decomposition by acids. The acid stability of BRL152 is equivalent to that of penicillin V at pH 2 and pH 3 when tested at temperatures of 5°C and 37°C.

Methods

Antibiotic concentrations in serum and in urine were determined by the cup-plate biological assay method using *Sarcina lutea* ATCC 9341 as test organism. Nutrient agar (Oxoid no. 2) was seeded with 5·0 ml. of an overnight broth culture per 500 ml. of agar and poured into large assay plates to give an agar depth of approximately 4 mm. Plugs of agar were removed to give holes of 7 mm. diameter which were filled with the solutions to be assayed. The plates were incubated at 37°C overnight. The ring diameters were then measured and the concentrations read off in the usual way from the standard line. Penicillin-V concentrations were assayed against a standard sample of potassium phenoxymethyl penicillin. Similarly, concentrations of BRL152 were assayed against standard solutions of 6 (*a*-phenoxypropionamido) penicillinate. Standards of 2·0, 1·0, 0·5, 0·25, 0·1, and 0·05 μg. per ml. were used on each assay plate. Standards and unknowns were so arranged on the plates as to compensate both for any variations in agar thickness and the time factor in filling the plate.

The samples to be assayed were diluted to give a concentration of approximately 0·5 μg. per ml. The diluent for the unknown samples and for the standard solutions was a 3·0% solution of bovine plasma albumin fraction V (Armour Pharmaceutical Co.) in *M*/20 phosphate buffer, pH 7·0. This solution was used for both BRL152 assays and penicillin-V assays, it having previously been found by experiment to have the same effect as human serum on the assays of these penicillins by this method.

* Marketed by Beecham Research Laboratories Limited under the registered trade mark 'Broxil'.

TABLE I—INDIVIDUAL SERUM CONCENTRATIONS IN EXPERIMENT 1 (BRL152)

Subject	Age	Sex	Weight (kg.)	Dose (mg.)	Route	State	Serum concentrations (μg. per ml.)			
							1 hr.	2 hr.	4 hr.	6 hr.
A	33	M	78	250	Oral	Fasting	2·28	0·82	0·02	0
B	26	M	76	250	Oral	Fasting	2·05	1·4	0·22	0·02
C	22	M	65	250	Oral	Fasting	2·74	0·7	0·06	0
D	26	M	85	250	Oral	Fasting	2·8	0·82	0·08	0
E	40	M	60	250	Oral	Fasting	10·0	3·16	0·38	0·06
F	27	M	95	250	Oral	Fasting	5·35	1·3	0·1	0
G	24	M	62	250	Oral	Fasting	3·5	1·0	0·09	0
H	24	F	55	250	Oral	Fasting	4·2	0·93	0·08	0
J	24	F	71	250	Oral	Fasting	3·3	0·51	0·04	0
K	20	F	60	250	Oral	Fasting	4·4	0·93	0·07	0

TABLE Ia—MEANS OF SERUM CONCENTRATIONS IN EXPERIMENT 1 (BRL152)

No. of subjects	Average age	Average weight (kg.)	Mean serum concentrations (μg. per ml.)			
			1 hr.	2 hr.	4 hr.	6 hr.
10	26·6	70·7	4·06	1·16	0·11	0·008

The Experiments

Experiment 1

10 unselected subjects, 7 males and 3 females, took part in this investigation. Their weights ranged between 55 and 85 kg. (average 70·7 kg.) and their ages between 20 and 40 years (average 26·6 years). All subjects were requested to fast from 10 P.M. the night before the investigation was carried out.

On the morning of the test a "zero time" sample of blood was taken from the median cubital vein. The subjects were then given 250 mg. of BRL152 as a freshly prepared *solution* in 20 ml. of water. The solution was taken as a single draught and followed by a further 50 ml. of water. The subjects then breakfasted. Blood samples were taken at 1, 2, 4, and 6 hours after the administration of the penicillin.

TABLE II—INDIVIDUAL SERUM CONCENTRATIONS IN EXPERIMENT 1 (K PENICILLIN V)

Subject	Age	Sex	Weight (kg.)	Dose (mg.)	Route	State	Serum concentrations (μg. per ml.)			
							1 hr.	2 hr.	4 hr.	6 hr.
A	33	M	78	250	Oral	Fasting	0·83	0·5	0·02	0
B	26	M	76	250	Oral	Fasting	0·88	0·33	0·01	0
C	22	M	65	250	Oral	Fasting	1·1	0·25	0·02	0
D	26	M	85	250	Oral	Fasting	1·58	0·29	0·03	0·01
E	40	M	60	250	Oral	Fasting	3·35	1·3	0·13	0·01
F	27	M	95	250	Oral	Fasting	0·82	0·031	0·03	0
G	24	M	62	250	Oral	Fasting	1·08	0·21	0·03	0
H	24	F	55	250	Oral	Fasting	2·5	0·48	0·02	0
J	24	F	71	250	Oral	Fasting	1·05	0·15	0·02	0
K	20	F	60	250	Oral	Fasting	1·44	0·22	0	0

TABLE IIa—MEANS OF SERUM CONCENTRATIONS IN EXPERIMENT 1 (K PENICILLIN V)

No. of subjects	Average age	Average weight (kg.)	Mean serum concentrations (μg. per ml.)			
			1 hr.	2 hr.	4 hr.	6 hr.
10	26·6	70·7	1·46	0·38	0·03	0·002

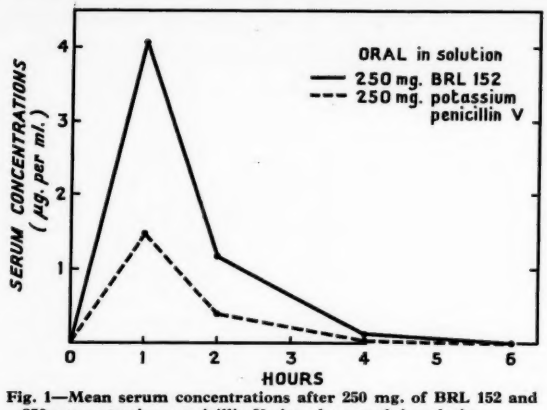


Fig. 1—Mean serum concentrations after 250 mg. of BRL 152 and 250 mg. potassium penicillin V given by mouth in solution.

In addition, zero to 6-hour urine samples were also collected from the 7 male subjects taking part in this experiment. The blood and urine samples were assayed for BRL152 on the same day as the test by the method already described.

The individual serum concentrations obtained in this experiment are shown in table I and their means in table Ia. It was found that a mean of 64% of the dose of BRL152 was excreted in the urine over the 6-hour period.

The procedure was repeated in exact detail on the same subjects, a few days later, using 250 mg. of the potassium salt of penicillin V (phenoxymethylpenicillin) in solution. The results of this investigation are shown in table II and the means in table IIa.

It was found in this experiment that a mean of 50% of the dose of potassium penicillin V was excreted in the 0–6-hour urine samples.

Fig. 1 shows graphically the comparative mean serum concentrations in μg. per ml. of BRL152 and the potassium salt of penicillin V.

In the 10 subjects investigated BRL152 produces serum concentrations at least twice those obtained with the potassium salt of penicillin V.

Serum concentrations of penicillin following oral loads in the form of powder (Juncher and Raaschou 1957) or as solutions may be quite different from those obtained when the *tablet* form of the penicillin is used. The blood concentrations obtained from tablet administration depend, among other things, upon the disintegration time for the respective tablets.

Experiment 2

10 unselected subjects, different from those in experiment 1 (5 males and 5 females), took part in this investigation.

Their weights ranged between 51 and 90 kg. (average 64·7 kg.) and their ages between 21 and 24 years (average 22 years).

The same procedure was adopted in this experiment as previously but in place of the solution, 250 mg. *tablets* of potassium penicillin V were administered. It was found, however, in this experiment that one of the subjects (subject L) was not in the fasting state and her results are not included in the means for this group.

Table III sets out the results obtained in the 10 subjects following the oral administration of 250 mg. tablets of potassium penicillin V and table IIIa the means of the 9 *fasting* subjects.

It was found that a mean of 40% of the dose of potassium penicillin V was excreted in the urine over the 0–6-hour period.

The procedure was repeated in the same 10 subjects substituting 250 mg. *tablets* of BRL152 in place of the potassium penicillin V tablets. Subject L who had previously appeared in the non-fasting state was requested to attend for this experiment also non-fasting.

Table IV sets out the results obtained in the 10 subjects in this experiment and table IVa the means of the 9 *fasting* subjects. The results are also shown in fig. 2.

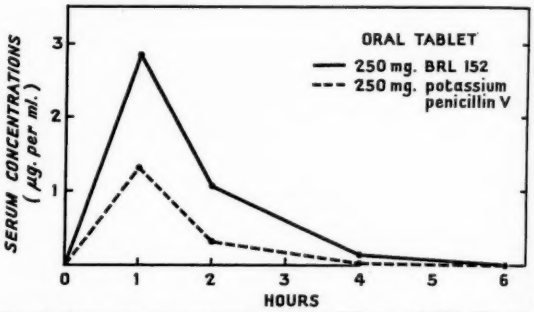


Fig. 2—Mean serum concentrations after 250 mg. of BRL 152 and 250 mg. potassium penicillin V given by mouth as tablet.

A mean of 60% of the dose of BRL152 was excreted in the urine over the 0–6-hour period.

In tablet form BRL152 produces serum concentrations of antibiotic approximately twice those obtained with potassium penicillin V.

Discussion

The absorption of oral penicillins tends to vary from subject to subject and often in the same subject at different

TABLE III—INDIVIDUAL SERUM CONCENTRATIONS IN EXPERIMENT 2 (K PENICILLIN V)

Subject	Age	Sex	Weight (kg.)	Dose (mg.)	Route	State	Serum concentrations (μg. per ml.)			
							1 hr.	2 hr.	4 hr.	6 hr.
L	24	F	52	250	Oral	Non-fasting	0·47	0·45	0·27	0·04
M	21	F	54	250	Oral	Fasting	1·63	0·29	0·01	0
N	21	F	60	250	Oral	Fasting	0·9	0·37	0·01	0
P	23	M	60	250	Oral	Fasting	1·46	0·13	0·01	0
Q	22	M	78	250	Oral	Fasting	0·8	0·72	0·13	0
R	21	F	59	250	Oral	Fasting	2·16	0·36	0·02	0
S	21	F	51	250	Oral	Fasting	1·0	0·26	0·04	0
T	23	M	71	250	Oral	Fasting	1·18	0·18	0·01	0
U	24	M	90	250	Oral	Fasting	1·69	0·39	0·06	0
V	22	M	72	250	Oral	Fasting	1·1	0·15	0·02	0

TABLE IIIa—MEANS OF SERUM CONCENTRATIONS IN EXPERIMENT 2 (K PENICILLIN V)

No. of subjects	Average age	Average weight (kg.)	Mean serum concentrations (μg. per ml.)			
			1 hr.	2 hr.	4 hr.	6 hr.
9	22	64·7	1·32	0·32	0·03	0

TABLE IV—INDIVIDUAL SERUM CONCENTRATIONS IN EXPERIMENT 2 (BRL152)

Subject	Age	Sex	Weight (kg.)	Dose (mg.)	Route	State	Serum concentrations (μg. per ml.)			
							1 hr.	2 hr.	4 hr.	6 hr.
L	24	F	52	250	Oral	Non-fasting	1·08	0·84	1·18	0·18
M	21	F	54	250	Oral	Fasting	3·0	1·3	0·09	0
N	21	F	60	250	Oral	Fasting	3·0	1·0	0·17	0
P	23	M	60	250	Oral	Fasting	2·43	0·9	0·11	0
Q	22	M	78	250	Oral	Fasting	2·23	0·74	0·1	0
R	21	F	59	250	Oral	Fasting	4·3	1·6	0·17	0
S	21	F	51	250	Oral	Fasting	2·0	1·52	0·26	0·09
T	23	M	71	250	Oral	Fasting	2·78	0·82	0·1	0
U	24	M	90	250	Oral	Fasting	1·88	0·74	0·12	0
V	22	M	72	250	Oral	Fasting	3·9	0·92	0·15	0

TABLE IVa—MEANS OF SERUM CONCENTRATIONS IN EXPERIMENT 2 (BRL152)

No. of subjects	Average age	Average weight (kg.)	Mean serum concentrations (μg. per ml.)			
			1 hr.	2 hr.	4 hr.	6 hr.
9	22	64·7	2·84	1·06	0·14	0·01

TABLE V—INDIVIDUAL SERUM CONCENTRATIONS IN EXPERIMENT 3 (BRL152)

Subject	Age	Sex	Weight (kg.)	Dose (mg.)	Route	State	Serum concentrations (μg. per ml.)			
							1 hr.	2 hr.	4 hr.	6 hr.
M	21	F	54	500	Oral	Fasting	12·5	6·9	0·66	0
P	23	M	60	500	Oral	Fasting	8·8	1·89	0·24	0
R	21	F	59	500	Oral	Fasting	13·0	4·7	0·39	0·06
T	23	M	71	500	Oral	Fasting	3·15	2·47	0·2	0
V	22	M	72	500	Oral	Fasting	6·0	2·0	0·44	0

TABLE Va—MEANS OF SERUM CONCENTRATIONS IN EXPERIMENT 3 (BRL152)

No. of subjects	Average age	Average weight (kg.)	Mean serum concentrations (μg. per ml.)			
			1 hr.	2 hr.	4 hr.	6 hr.
5	22	63	8·7	3·6	0·4	0·01

times. Better absorptions are usually obtained in the fasting rather than in the postprandial state.

Although it will be appreciated that the number of subjects taking part in these initial experiments is small (20) and that they are all in the younger age-group, there can be little doubt that the absorption of BRL152 is superior to that of potassium penicillin V.

The proportion of the dose of penicillin which is excreted in the urine is probably one of the best indices of absorption, assuming similar metabolic pathways for the various penicillins. Some 95% of the penicillin excreted in the urine following an oral load is excreted in the 0–6-hour fraction. Heatley (1956) found that a larger and more constant proportion of the dose is excreted in the urine after oral administration of penicillin V than after *oral* penicillin G. It will be seen from the comparative excretions over the 0–6-hour periods in the above experiments that there is a greater percentage of the dose excreted in the urine following BRL152 than following potassium penicillin V. This data supports the serum concentrations and confirms the better absorption of BRL152.

Experiment 3

5 subjects from the previous experiment (i.e., subjects M, P, R, T, and V) were given 500 mg. of BRL152 under the same conditions as previously.

Table V sets out the serum concentrations obtained in this experiment and table Va shows the average for the 5. Table VI sets out for comparative purposes the average of the 5 subjects following the oral administration of 250 mg. of BRL152 in experiment 2. Table VIa shows the means.

Fig. 3 shows the results obtained with the 250 mg. and 500 mg. doses of BRL152 in these 5 subjects. It will be seen from the graph that for doses of 250 and 500 mg. doubling the dose results in twice the serum concentrations.

TABLE VII—INDIVIDUAL SERUM CONCENTRATIONS IN EXPERIMENT 4 (BRL152)

Subject	Age	Sex	Weight (kg.)	Dose (mg.)	Route	State	Serum concentrations (μg. per ml.)			
							1 hr.	2 hr.	4 hr.	6 hr.
C	22	M	65	125	Oral	Fasting	0·81	0·22	0	0
F	27	M	95	125	Oral	Fasting	0·84	0·34	0·11	0
G	24	M	62	125	Oral	Fasting	1·3	0·39	0·1	0
H	24	F	55	125	Oral	Fasting	1·42	0·34	0	0
J	24	F	71	125	Oral	Fasting	0·72	0·31	0	0

TABLE VIIa—MEANS OF SERUM CONCENTRATIONS IN EXPERIMENT 4 (BRL152)

No. of subjects	Average age	Average weight (kg.)	Mean serum concentrations (μg. per ml.)			
			1 hr.	2 hr.	4 hr.	6 hr.
5	24	70	1·02	0·32	0·04	0

TABLE VI—COMPARABLE FIGURES FROM EXPERIMENT 2 (BRL152)

Subject	Age	Sex	Weight (kg.)	Dose (mg.)	Route	State	Serum concentrations (μg. per ml.)			
							1 hr.	2 hr.	4 hr.	6 hr.
M	21	F	54	250	Oral	Fasting	3·0	1·3	0·09	0
P	23	M	60	250	Oral	Fasting	2·43	0·9	0·11	0
R	21	F	59	250	Oral	Fasting	4·3	1·6	0·17	0
T	23	M	71	250	Oral	Fasting	2·78	0·82	0·1	0
V	22	M	72	250	Oral	Fasting	3·9	0·92	0·15	0

TABLE VIa—COMPARABLE MEANS FROM EXPERIMENT 2 (BRL152)

No. of subjects	Average age	Average weight (kg.)	Mean serum concentrations (μg. per ml.)			
			1 hr.	2 hr.	4 hr.	6 hr.
5	22	63	3·28	1·11	0·12	0

Experiment 4

In view of the comparative serum concentrations following the 250 mg. and 500 mg. oral dose of BRL152, it was decided to compare the figures obtained from a 125 mg. dose of BRL152 with those obtained from the 250 mg. dose in 5 of the subjects in experiment 1 (subjects C, F, G, H, and J). The subjects were given 125 mg. of BRL152 orally, and blood samples taken as in the previous experiments. The results are shown in table VII and the means in table VIIa. The comparative figures

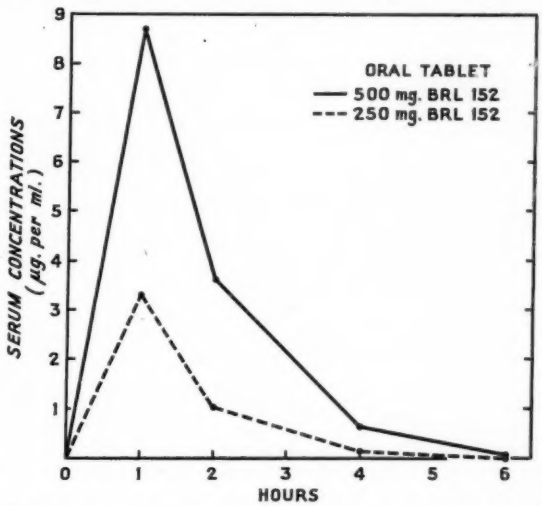


Fig. 3—Mean serum concentrations after 500 mg. and 250 mg. of BRL 152 given by mouth as tablet.

TABLE VIII—COMPARABLE FIGURES FROM EXPERIMENT 1 (BRL152)

Subject	Age	Sex	Weight (kg.)	Dose (mg.)	Route	State	Serum concentrations (μg. per ml.)			
							1 hr.	2 hr.	4 hr.	6 hr.
C	22	M	65	250	Oral	Fasting	2·74	0·7	0·06	0
F	27	M	95	250	Oral	Fasting	5·35	1·3	0·1	0
G	24	M	62	250	Oral	Fasting	3·5	1·0	0·09	0
H	24	F	55	250	Oral	Fasting	4·2	0·93	0·08	0
J	24	F	71	250	Oral	Fasting	3·3	0·51	0·04	0

TABLE VIIIa—COMPARABLE MEANS FROM EXPERIMENT 1 (BRL152)

No. of subjects	Average age	Average weight (kg.)	Mean serum concentrations (μg. per ml.)			
			1 hr.	2 hr.	4 hr.	6 hr.
5	24	70	3·82	0·89	0·07	0

TABLE IX—INDIVIDUAL SERUM CONCENTRATIONS IN EXPERIMENT 5 (BRL152)

Subject	Age	Sex	Wt. (kg.)	Dose (mg.)	Route	State	Serum concentrations (μg. per ml.)				
							½ hr.	1 hr.	2 hr.	4 hr.	6 hr.
A	20	M	62	500	Oral	Fasting	1·14	1·86	2·0	0·49	0·05
B	23	M	68	500	Oral	Fasting	8·3	2·65	0·65	0·06	0
C	21	M	68	500	Oral	Fasting	5·0	6·1	1·46	0·34	0·09
D	21	M	75	500	Oral	Fasting	2·71	3·65	2·0	0·36	0·08

TABLE IXa—MEANS OF SERUM CONCENTRATIONS IN EXPERIMENT 5 (BRL152)

No. of subjects	Average age	Average weight (kg.)	Serum concentrations (μg. per ml.)				
			½ hr.	1 hr.	2 hr.	4 hr.	6 hr.
4	21	68	4·29	3·57	1·53	0·31	0·05

TABLE X—INDIVIDUAL SERUM CONCENTRATIONS IN EXPERIMENT 5 (K PENICILLIN V)

Subject	Age	Sex	Wt. (kg.)	Dose (mg.)	Route	State	Serum concentrations (μg. per ml.)				
							½ hr.	1 hr.	2 hr.	4 hr.	6 hr.
A	20	M	62	500	Oral	Fasting	2·5	2·1	0·66	0·08	0
B	23	M	68	500	Oral	Fasting	4·1	1·4	0·29	0·06	0
C	21	M	68	500	Oral	Fasting	2·6	1·7	0·88	0·09	0
D	21	M	75	500	Oral	Fasting	1·4	3·6	1·22	0·43	0

TABLE Xa—MEANS OF SERUM CONCENTRATIONS IN EXPERIMENT 5 (K PENICILLIN V)

No. of subjects	Average age	Average weight (kg.)	Serum concentrations (μg. per ml.)				
			½ hr.	1 hr.	2 hr.	4 hr.	6 hr.
4	21	68	2·65	2·2	0·76	0·17	0

for the 250 mg. dosage are in table VIII and the means in table VIIIa.

It can be considered that in the dose range of 125 mg. to 500 mg. doubling the dose produces at least double the serum concentrations.

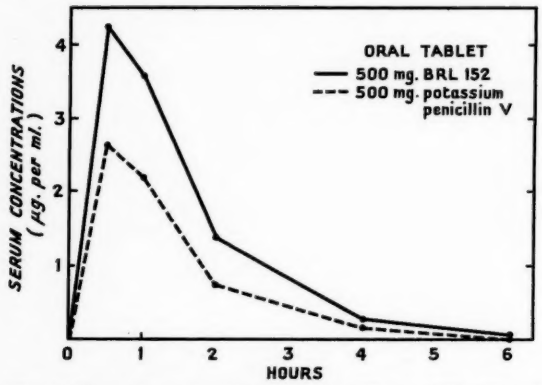


Fig. 4—Mean serum concentrations after 500 mg. BRL 152 and 500 mg. potassium penicillin V given by mouth as tablet.

Experiment 5

500 mg. of BRL152 was compared with 500 mg. of potassium penicillin V by mouth in a further 4 subjects. Their average age was 21 and their average weight was 68 kg.

It was decided in this experiment to take a ½-hour blood sample in addition to the usual 1, 2, 4, and 6 hour specimens, to determine whether the peak concentrations were obtained earlier than 1 hour.

Table IX shows the individual results obtained following the oral administration of 500 mg. of BRL152 and table IXa the means of 4.

Table X sets out the individual results following the oral administration of 500 mg. of potassium penicillin V and table Xa the means of these results. The results are shown in fig. 4.

Although the subjects as a group would appear to be poor absorbers, the serum concentrations of BRL152 are still twice those of potassium penicillin V.

It will also be seen that in 1 subject the peak was found at ½ hour, in 2 subjects at 1 hour, and in the other at 2 hours following the dose. This variation on the times of obtaining peak serum concentrations stimulated our interest in obtaining more exact information as to the rate of absorption of BRL152 and the following experiment was carried out.

Experiment 6

2 subjects were given 250 mg. of BRL152 orally. 5-minute blood samples were obtained by means of indwelling Guest's needles for a period of 1 hour after administration of the drug. At the end of the 1-hour period, samples were then taken ½ hourly up to 2 hours.

1 subject was also given 250 mg. of BRL152 and 10-minute samples were obtained by venepuncture for a period of 1 hour and then ½ hourly up to 2 hours. The results are shown in table XI and in fig. 5.

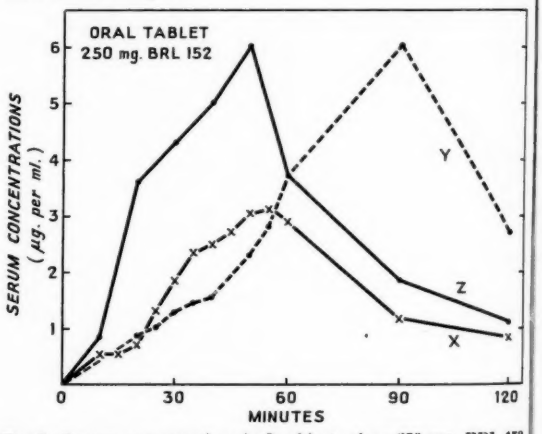


Fig. 5—Serum concentrations in 3 subjects given 250 mg. BRL 152 by mouth as tablet. 5-minute samples were taken from X and Y for the first hour, then ½-hourly 10-minute samples were taken from Z for the first hour, then ½-hourly.

Table XI shows that the rates of absorption vary in the individual, and peak concentrations are obtained at different times.

If only the ½, 1, and 2 hour samples were considered, the

TABLE XI—INDIVIDUAL SERUM CONCENTRATIONS IN EXPERIMENT 6 (BRL152)

Subject	Age	Sex	Wt. (kg.)	Dose (mg.)	Route	State	Serum concentrations (μg. per ml.)											
							5 min.	10 min.	15 min.	20 min.	25 min.	30 min.	35 min.	40 min.	45 min.	50 min.	55 min.	60 min.	90 min.	120 min.
X	24	F	71	250	Oral	Fasting	<0·5	0·53	0·55	0·73	1·3	1·85	2·35	2·45	2·7	3·0	3·1	2·9	1·2	0·8
Y	24	F	55	250	Oral	Fasting	<0·5	<0·5	<0·5	0·88	1·03	1·25	1·45	1·55	..	2·3	2·8	3·7	6·0	2·7
Z	30	M	71	250	Oral	Fasting	..	0·85	3·6	..	..	4·3	..	5·0	..	6·0	..	3·7	1·85	1·1

TABLE XII—INDIVIDUAL SERUM CONCENTRATIONS IN EXPERIMENT 7 (BRL152)

Subject	Age	Sex	Wt. (kg.)	Dose (mg.)	Route	State	Serum concentrations (μg. per ml.)				
							¼ hr.	½ hr.	1 hr.	1½ hr.	2 hr.
O	20	F	53	250	Oral	Fasting	..	6·85	2·3	..	0·45
W	33	M	78	250	Oral	Fasting	2·23	3·8	4·2	1·85	0·75
X	24	F	71	250	Oral	Fasting	0·55	1·85	2·9	1·2	0·8
Y	24	F	55	250	Ora.	Fasting	0	1·25	3·7	6·0	2·7
Z	30	M	71	250	Oral	Fasting	3·6	4·3	3·7	1·85	1·1
Mns.	26	..	65·2	250	Oral	Fasting	1·6	3·6	3·36	2·72	1·16

TABLE XIIa—INDIVIDUAL SERUM CONCENTRATIONS IN EXPERIMENT 7 (Na PENICILLIN G)

Subject	Age	Sex	Wt. (kg.)	Dose (units)	Route	State	Serum concentration (μg. per ml.)			
							¼ hr.	½ hr.	1 hr.	1½ hr.
O	20	F	53	400,000	I.M.	Mobile	3·37	3·52	1·5	1·1
W	33	M	78	400,000	I.M.	Mobile	2·83	2·69	0·93	0·58
X	24	F	71	400,000	I.M.	Mobile	4·05	4·23	1·27	0·56
Y	24	F	55	400,000	I.M.	Mobile	4·17	3·65	1·9	1·01
Z	30	M	71	400,000	I.M.	Mobile	2·37	2·05	1·6	0·88
Means	26	..	65·2	400,000	I.M.	Mobile	3·36	3·23	1·44	0·83

means would be found to be 2·47, 3·4, and 1·5 μg. per ml. respectively with a maximum peak of 3·4 μg. per ml. If, however, peak concentrations only are considered the means for these would be 5·0 μg. per ml. It would appear then that figures obtained from the more classical time intervals of blood-sampling do not necessarily reflect the true pattern of absorption.

Preliminary Comparison of Oral BRL152 with Intramuscular Penicillin G

It is generally appreciated that the oral absorption of penicillin varies between individuals and frequently in the same individual from time to time. It is generally considered that intramuscular injections of penicillin provide the most reliable route for obtaining satisfactory serum concentrations of penicillin. The absorption of a penicillin, however, from an intramuscular injection may also vary; it depends to a large extent upon the degree of protein binding, state of the circulation, the mobility of the subject, &c. With a subject completely at rest, there may be a delay of over half an hour or more before detectable amounts of penicillin appear in the blood.

In addition, the serum concentrations following a given intramuscular injection of sodium penicillin G in comparable subjects is by no means constant. In view of the variability of both oral and intramuscular administration of penicillin, it was decided to compare oral BRL152 weight for weight with sodium penicillin G by the intramuscular route.

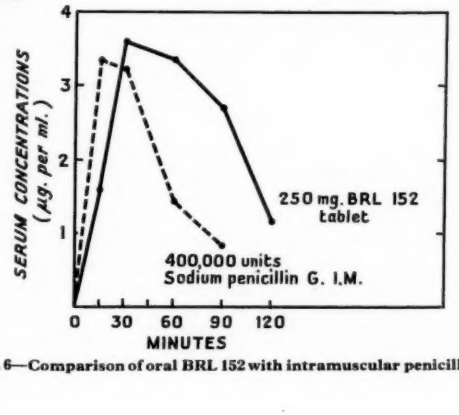


Fig. 6—Comparison of oral BRL 152 with intramuscular penicillin G.

Experiment 7

400,000 units (approximately 250 mg.) of the sodium salt of penicillin G was given by intramuscular injection to 5 subjects (X, Y, and Z, table XI, and 2 new subjects O and W). Venous samples were taken at ¼, ½, 1, and 1½ hours following the injection. The results were compared with serum concentrations obtained in these subjects from 250 mg. tablets of BRL152 by mouth.

Table XII sets out the results obtained from the 250 mg. load of BRL152 and table XIIa the results with intramuscular penicillin G. Fig. 6 illustrates graphically the results of this comparison. The total antibiotic concentration of BRL152 over the period of study is, at the very least, equal to that following the approximately equivalent weight of sodium penicillin G by intramuscular injection.

This preliminary study on BRL152 has been carried out in subjects of the younger age-group. Further work in a wider age range will be reported later.

Conclusions

(1) Absorption studies on the potassium salt of 6 (*a*-phenoxypropionamido) penicillanic acid (BRL152) showed that it is well absorbed and that it produces serum concentrations at least twice those obtained with equivalent doses of the potassium salt of penicillin V (phenoxymethylpenicillin).

(2) Urinary excretion studies confirm the superior absorption of BRL152.

(3) Doubling the dose of BRL152 in the 125 mg.–500 mg. range results in doubling the serum concentrations.

(4) Serum concentrations following the oral administration of BRL152 are at least equal to those obtained following the intramuscular injection of approximately equivalent weights of the sodium salt of crystalline penicillin G.

We wish to thank the volunteers for their enthusiastic cooperation, Mrs. S. Stevens and her staff for carrying out the assays, and Miss J. Crawford and others for their help in the preparation of this paper.

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PERCUTANEOUS INTRODUCTION OF CARDIAC PACEMAKER ELECTRODE

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THE treatment of complete heart-block after open-heart surgery is to some extent eased by the use of an electric artificial pacemaker (see figure), the electrodes being placed at operation and removed only when a suitable ventricular rate has become established or when the conduction mechanism has recovered (Weirich et al. 1958).

The pacemaker is now commonly used when atrio-ventricular block is recognised while the chest is still open and the heart in view. Sometimes, however, the onset of complete heart-block is delayed and the idio-ventricular rate falls dangerously low during the post-operative period. If then the heart fails to respond to drugs, immediate restoration of an adequate ventricular rate by means of the pacemaker is essential.

In such an emergency, the cardiac electrode can be satisfactorily placed by percutaneous ventricular puncture

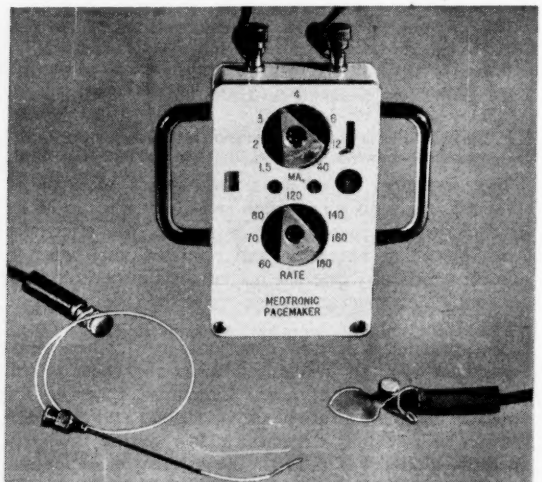
(Thevenet et al. 1958). This allows all the advantages of direct monopolar ventricular stimulation without resort to thoracotomy for the sole purpose of placing the cardiac electrode. During the past six months, at the San Francisco-Stanford Hospital, we have seen two examples of sudden complete heart-block of delayed onset following open-heart surgery. Experience with an external pacemaker (Zoll et al. 1955) has been limited to a non-surgical case, when the disadvantages of this method (Brockman et al. 1958, Weirich et al. 1958) were observed.

Case-reports

Case 1.—In the first patient, complete heart-block developed ten hours after closure of an ostium primum defect. At the end of the operation normal sinus rhythm had been present, and the median sternotomy wound was reopened for introduction of the myocardial electrode. The patient subsequently recovered, although heart-block persisted.

Case 2.—A 14-year-old boy with transposition of the great vessels and a common ventricle underwent exploratory ventriculotomy, but no repair was possible. Varying degrees of incomplete heart-block had been present from the time of induction of anæsthesia, and, as conduction was steadily improving, pacemaker electrodes were not placed at surgery. After operation, rectal isoprenaline was started and a ventricular rate of 80–90 per min. maintained without difficulty. By the morning of the second postoperative day atrioventricular block had become complete, and the ventricular rate began to slow progressively despite increasing isoprenaline dosage. During the forenoon of the fourth postoperative day the rate fell more rapidly until it reached 35 per minute, at which stage respiration (inspiration) and the heart-beat became synchronous. There were two episodes of transitory unconsciousness. A single large dose of isoprenaline intravenously (200 μg.) increased the ventricular rate to 55 per minute for five minutes, after which it again slowed progressively. Institution of the pacemaker became urgent.

Introduction of the cardiac electrode by reopening the chest seemed unsafe in these circumstances. It was decided to place the electrode by percutaneous ventricular puncture. At the bedside, under sterile conditions, the indifferent electrode was implanted subcutaneously in the epigastrium, and the myocardial wire electrode was directed into the ventricular chamber through a no. 16 hollow-bore needle inserted in the fifth intercostal space, $3^1/_4$ in. from the midline. The inserting needle was removed and, with the pacemaker turned on, the electrode was withdrawn until the heart-rate became that of the pacemaker impulse, indicating that the bare wire of the electrode was in contact with myocardium. The current amplitude was then adjusted to be just above threshold level, and the wire fixed by a single skin suture tied round it. The electrical pacemaker controlled ventricular rate for twenty-seven hours, by which time a satisfactory idioventricular rate had returned. The electrodes were removed after fifty-seven hours. There was no clinical or radiographic evidence of bleeding from the puncture wound in the heart; and the patient recovered well, with disappearance of complete heart-block on the sixteenth postoperative day.



Transistor pacemaker with myocardial electrode (left) and indifferent electrode (right). The usual curved needle for myocardial suture has been removed and the wire electrode passed through a no. 16 needle preparatory to placement by ventricular puncture.

Conclusion

As an emergency measure, placement of a cardiac electrode by percutaneous ventricular puncture has proved quick and effective in the treatment of heart-block following operations on the heart. This procedure may prove useful in the management of heart-block due to other causes.

We wish to express our appreciation to Dr. Frank Gerbode for his guidance in the preparation of this communication.

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THE LIVER IN ULCERATIVE COLITIS
TREATMENT OF PERICHOLANGITIS WITH TETRACYCLINE

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IN a previous paper (Boden et al. 1959) 11 cases of pericholangitis were reported in which this condition was considered to be the result of portal bacteræmia associated with non-specific ulcerative colitis. It was suggested that antibiotics should be effective in treating this type of liver disease, provided the offending organism was sensitive. We describe here the preliminary results of treatment with tetracycline.

Material

5 patients have been receiving tetracycline, 500 mg. daily, for from one to ten months. In all patients pericholangitis was chronic and progressive, the diagnosis being based on the microscopic appearance of tissue obtained by percutaneous liver biopsy, and on liver-function tests which indicated an obstructive lesion. Of these patients cases 1–3 have been reported previously (Boden et al. 1959, cases 1, 2, and 4). 2 detailed case-records are given here as examples of our results.

* Supported by a grant from an anonymous donor.

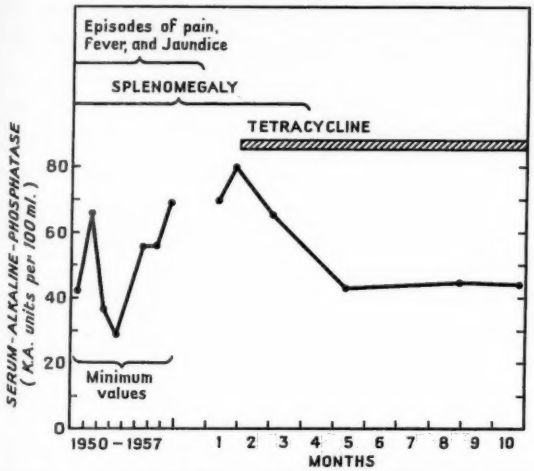

Fig. 1—Case 1: yearly minimum values of serum-alkaline-phosphatase in 1950–57 and values over the ten-month period of tetracycline administration in 1958–59.

Case-reports

Case 1.—A man, aged 40, had had clinical evidence of liver disease for twenty-seven years. Since the onset of colitis he had had attacks of diarrhœa with fever, jaundice, and abdominal pain at least every four to five months, and hepatosplenomegaly had been constant since he was first seen in 1950. Oral tetracycline, 500 mg. daily, was commenced in September, 1958, and has now been continued for ten months. Over this period he has had no further episodes of abdominal pain, fever, and jaundice, and at the end of three months' treatment the spleen was no longer palpable. Fig. 1 shows the range of serum-alkaline-phosphatase over the period 1950–59. There had been a continuous rise in the yearly minimum level of serum-alkaline-phosphatase over the five years preceding the commencement of tetracycline, but over the subsequent four months the level fell from 80 to 44 King-Armstrong (K.A.) units per 100 ml., around which it remained.

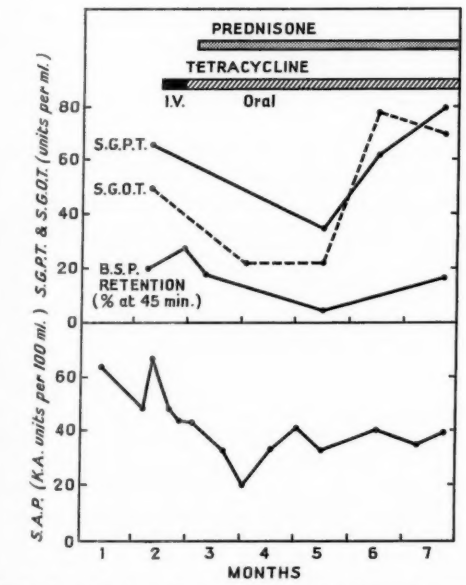

Fig. 2—Case 4: values of serum-alkaline-phosphatase, bromsulphalein retention, and serum-glutamic-oxaloacetic transaminase and serum-glutamic-pyruvic-transaminase before and during the period of administration of tetracycline and prednisone.

Case 4.—A girl, aged 19, presented with a three-year history of ulcerative colitis in which the initial episode, of three weeks' duration, had been moderately severe, but the symptoms since then mild and intermittent. She was first seen during an exacerbation of colitis seven months ago, when a granular mucosa was found on sigmoidoscopy. Investigations revealed hæmoglobin 10·8 g. per ml., white blood-cells 11,000 per c.mm., total serum-bilirubin 0·6 mg. per 100 ml., serum-alkaline-phosphatase 64 K.A. units, thymol flocculation 3+, zinc-sulphate turbidity 17 units, and bromsulphalein retention 20% at forty-five minutes. Barium-enema examination showed ulcerative colitis involving the bowel distal to the hepatic flexure. Liver biopsy showed an inflammatory infiltrate in the portal tracts with no evidence of fibrosis or hepatic parenchymal degeneration. Tetracycline was given intravenously as tyrrolidinonethyl tetracycline ('Reverin') 500 mg. daily for ten days, followed by oral tetracycline 500 mg. daily for six months up until the present. During the first two weeks of therapy a severe exacerbation of colitis occurred which responded to 40 mg. of prednisone daily, with gradual reduction to the present level of 10 mg. daily. Fig. 2 summarises the treatment, and levels of serum-alkaline-phosphatase, bromsulphalein retention, and serum-transaminases over this period. After six weeks the serum-alkaline-phosphatase had fallen to 20 K.A. units, this improvement being paralleled by a fall in transaminases and bromsulphalein retention. Over the next month the serum-alkaline-phosphatase rose again to 41 K.A. units and since then has fluctuated between 35 and 40 units. Despite these abnormalities of serum-alkaline-phosphatase, the serum-transaminases and bromsulphalein-retention values were all normal after three months. Subsequently these latter tests have again become abnormal.

This case illustrates pericholangitis in a subclinical form, as at no time has there been any historical or clinical evidence of liver disease.

Discussion

5 patients with pericholangitis have shown an improvement in liver-function tests, with a fall in serum-alkaline-phosphatase, during the period of administration of tetracycline. Clinical improvement was seen in cases 1 and 2, who had clinical evidence of liver disease when treatment was started. In case 4, which was one of subclinical pericholangitis, improvement in liver function followed the start of treatment with tetracycline and continued after the administration of predisone; and the only abnormality at one stage was slight elevation of the serum-alkaline-phosphatase. It may be suggested that the biochemical improvement was due to the prednisone; but corticotrophin did not improve case 2, nor prednisone a similar case reported by Goldgraber and Kirsner (1959). In case 1 the clinical improvement, with no recurrence of jaundice, pain, and fever, and with reduction in the size of the spleen, was paralleled by improvement in liver function with a fall in serum-alkaline-phosphatase. In cases 1 and 4 the levels of serum-alkaline-phosphatase appear to have settled at relatively constant values after initial improvement.

That pericholangitis in ulcerative colitis is caused by bacterial infection is supported by the response of our patients to tetracycline.

Evidence of the bacterial basis of pericholangitis resulting from portal bacteræmia associated with unspecified ulcerative intestinal disease is contained in the report by Rachmilewitz (1951) on the effect of sulphonamides on the clinical manifestation of chronic intrahepatic cholangitis.

He described 5 patients who had episodes of pain in the right hypochondrium associated with fever and jaundice. Of

these, 4 had had a history of diarrhœa before the onset of liver disease; there was no evidence of extrahepatic biliary obstruction, and the livers showed the changes of pericholangitis. All 5 cases responded dramatically to sulphonamides with a fall in temperature, decrease in jaundice and other evidence of biliary obstruction, and in 2 loss of ascites. Relapses followed cessation of sulphonamides, and later courses did not always bring about similar dramatic improvement.

In patients on continuous antibiotic therapy for pericholangitis failure to respond beyond a certain point or to relapse would imply the development of bacterial immunity to the antibiotics. Resistant organisms could develop in either the established hepatic lesions or the colon so that fresh lesions could occur in the liver.

In all 5 of the present cases bowel flora resistant to tetracycline have developed. In case 5 an *Escherichia coli* resistant to tetracycline was obtained from the duodenal juice following pancreozymin stimulation, whilst in case 2 a coagulase-negative staphylococcus resistant to tetracycline was cultured from liver biopsy specimens.

Pericholangitis may persist because of failure of the hepatic lesions to heal after an episode of bacteræmia, or because of continuous or intermittent bacteræmia. Case 3 of Boden et al. (1959) supports the view that pericholangitis persists long after the cessation of portal bacteræmia. This patient underwent total colectomy in 1953 and abdominoperineal resection of the rectum in 1955. Now, four years later, her level of serum-alkaline-phosphatase is still elevated at 33 K.A. units, with thymol flocculation 3+ and zinc-sulphate turbidity 14 units.

In the relatively few patients with ulcerative colitis in whom pericholangitis develops, this complication may be determined either by hypersensitivity to bowel flora, so that minimal bacteræmia produces a significant inflammatory response in the liver, or defective host resistance. Evidence of bacterial hypersensitivity was seen in case 3, who had had skin lesions suggestive of a focal allergic angiitis which responded to the administration of tetracycline.

Long-term tetracycline was given in order to produce an effective blood-level to counter portal bacteræmia, and also to reduce established pericholangitis. Low dosage was chosen in an attempt to reduce side-effects, and only case 4 had a period of more intensive treatment—intravenous tetracycline for ten days.

Treatment should aim at eradicating established hepatic infection and preventing fresh lesions. This could be achieved by combining an intensive course of antibiotics lasting from four to six weeks (preferably using more than one drug, and including a bactericidal agent) with the long-term administration of antibiotics in smaller doses.

The organisms responsible for pericholangitis might be isolated directly by culturing a percutaneous liver biopsy specimen or indirectly from the duodenal juice after biliary stimulation with pancreozymin. The former method was tried in cases 2 and 5, and in case 2 a coagulase-negative staphylococcus resistant to tetracycline was obtained from two biopsies. In cases 1, 2, and 5 organisms were obtained from the duodenum—in case 1 *Streptococcus fæcalis*, in case 2 *Str. fæcalis* and *Esch. coli*, and in case 5 *Esch. coli*. In case 1 the same organism was obtained from the biliary tree at laparotomy. If pericholangitis was being perpetuated by intermittent or continuous bacteræmia, then culture and sensitivity of fæcal bacteria might give an indirect guide as to which antibiotic to administer. This would be an easy method of following altering patterns of intestinal bacteria and their sensitivity during long-term therapy. All 5 of the present cases now have fæcal organisms resistant to tetracycline.

Finally there is the problem of whether medical treatment has anything to offer in the long-term management of this condition, which, untreated, has been seen to progress to biliary cirrhosis (Boden et al. 1959). The difficulties associated with treatment are the persistence of the source of infection in the colon, altering bacterial flora and sensitivity, and the complications associated with antibiotic administration. In the presence of chronic, progressive pericholangitis it seems likely that the most effective method of halting progression and bringing about resolution would be to follow a short term of intensive antibiotic therapy by ileostomy and proctocolectomy.

Summary

Tetracycline was given over a long period to 5 patients with pericholangitis and ulcerative colitis in an attempt to counter portal bacteræmia and reverse the hepatic lesions.

Clinical and biochemical evidence suggests that this treatment was effective.

Lack of continued improvement, or relapse after initial improvement, can be attributed to altering bacteria or bacterial sensitivity.

The administration of effective antibiotics might be based on the sensitivity of organisms obtained by percutaneous liver biopsy, by duodenal intubation with pancreozymin stimulation, or from the stools.

In view of the difficulties associated with long-term antibiotic administration and the possibility of progression of pericholangitis to biliary cirrhosis, initial antibiotic therapy followed by an ileostomy and proctocolectomy probably gives the best chance of cure.

We wish to thank Prof. C. R. B. Blackburn for his encouragement and advice, and the members of the Fairfax Institute of Pathology and the Hallstrom Institute of Cardiology and Dr. T. D. Orban for performing the necessary investigations.

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BACTERIOLOGY OF LOWER-RESPIRATORY-TRACT SECRETIONS, SPUTUM, AND UPPER-RESPIRATORY-TRACT SECRETIONS IN "NORMALS" AND CHRONIC BRONCHITICS

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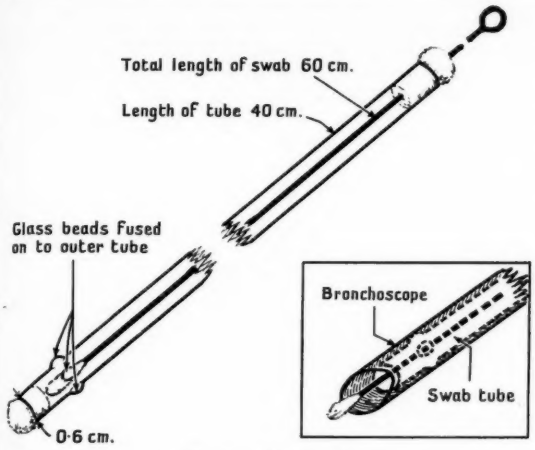
IN recent years there has been much interest in antibiotic therapy for chronic bronchitis, and this has led to an increasing demand for bacteriological examination of sputum and to technical refinements in carrying this out (May 1953a, Rawlins 1953). It has been suggested, however, that despite careful sampling methods, the bacteriology of sputum may be a misleading guide to the bacteriology of the bronchial tree, since sputum may be contaminated with upper-respiratory-tract secretions (Brumfitt et al. 1957). In the following investigation, therefore, specimens of bronchial secretions, sputum, and



The bronchial swab.

upper-respiratory-tract secretions obtained from symptomless patients with minimal pulmonary tuberculosis and from patients with chronic bronchitis were cultured so that the results could be compared. Specimens of bronchial secretions were recovered by bronchial swabbing, using a special technique to prevent contamination of the swabs with upper-respiratory-tract secretions.

Material and Methods

14 patients with small, healing, tuberculous lung lesions and 28 patients with chronic bronchitis were studied. The tuberculous patients were symptomless, but like many " normal " subjects were able to cough up a little sputum in the morning; none of them had ever suffered from bronchitis, and for convenience they will be referred to as normals.

In the patients with chronic bronchitis the diagnosis was based on a history of persistent cough, sputum production, dyspnœa apparently attributable only to disordered pulmonary function, and increased resistance to expiratory air-flow as shown by wheezing and timed vital-capacity tests.

A nasal swab, throat swab, and specimens of sputum and saliva were obtained from each patient. Bronchial swabbing was then carried out using a special technique. The bronchial swab is illustrated in the accompanying figure. It consists of a cottonwool swab on the end of a wire 60 cm. long contained in a glass carrier tube with four small glass beads fused on to its outer circumference at equidistant points 1 cm. from its end. The swab tube is firmly plugged with cottonwool at both ends, and the whole is wrapped in ' Kraft ' paper and sterilised by autoclaving at 15 lb. per sq. in. for twenty minutes. For use, the distal cottonwool plug is removed, and the swab and carrier are passed down a bronchoscope with the swab retracted. The glass beads prevent the open end of the carrier tube coming into contact with any bronchial secretions present on the inner wall of the bronchoscope. The swab is extruded by pushing it through the open end of the carrier tube, and the bronchial mucosa is swabbed under direct vision. Before bronchoscopy the patient is premedicated with gr. $^1/_3$ ' Omnopon ' by injection and given a 1 mg. tablet of amethocaine to suck in order to anæsthetise the mouth and pharynx. Lest anæsthetisation of the larynx should allow the passage of upper-respiratory secretions into the bronchial tree, the patient is kept tilted head-downwards. After swabbing has been carried out, the swab is retracted and removed in its carrier from the bronchoscope. The open distal end of the carrier tube is immediately re-plugged with sterile cottonwool pending bacteriological examination.

TABLE I—POTENTIAL PATHOGENS IN 14 " NORMAL " SUBJECTS

Specimens		No. in which potential pathogens were isolated					
Nature	No.	Any pathogen	*H. infl.*	Pneumo.	Coag. + staph.	Hæm. strep.	Colif.
Bronchial swab	14	0	0	0	0	0	0
Sputum ..	14	12	4	8	0	8	2
Upper resp. tract	14	14	4	10	5	8	3

Bacteriological Technique

Special care was taken to sample sputum adequately. Preliminary trials of pancreatin digestion on the lines described by Rawlins (1953) indicated that the method had no advantages over careful selection of purulent and/or mucoid portions of sputum. The direct sampling method was, therefore, adopted.

Within one hour of collection, samples from all sites were inoculated on to blood-agar plates, which were incubated at 37°C in an atmosphere of 5–10% carbon dioxide for eighteen to twenty-four hours. This enhanced the growth and mucoid characteristics of pneumococci while also allowing the preliminary identification of staphylococci, streptococci, *Hæmophilus influenzæ*, and coliform organisms. At the same time, all specimens were inoculated on to nutrient-agar plates containing 5% Fildes peptic digest of blood and 1 : 500,000 crystal-violet. Incubation was carried out at 37°C for eighteen to twenty-four hours in air. In this way growth of *H. influenzæ* was enhanced.

The further identification of bacterial types proceeded on standard lines. Pneumococci were classified as such on the results of bile solubility and/or " optochin " testing. Typing of streptococci was confined to identifying Lancefield group-A strains, using bacitracin (Maxted 1953). The presence of staphylococci was reported only if a strain produced coagulase on tube-testing. *H. influenzæ* was preliminarily identified by colonial and microscopical appearances. The ability of strains to grow only in the presence of blood was confirmed on subculture. Typing of capsulated strains by antisera to Pittman types a–f was carried out by slide agglutination. Gram-negative coliform bacilli were identified by their colonial appearances on blood-agar and by their ability to grow on McConkey agar: no further identification procedures were carried out.

TABLE II—POTENTIAL PATHOGENS IN 28 PATIENTS WITH CHRONIC BRONCHITIS

Specimens		No. in which potential pathogens were isolated					
Nature	No.	Any pathogen	*H. infl.*	Pneumo.	Coag. + staph.	Hæm. strep.	Colif.
Bronchial swab	28	23	15	9	1	1	3
Sputum ..	28	25	17	11	2	7	3
Upper resp. tract	28	26	10	15	3	10	5

Results

Table I shows the distribution of potential pathogens in bronchial swabs, sputum, and upper-respiratory-tract secretions in the 14 " normal " subjects.

Table II shows the distribution of potential pathogens in bronchial swabs, sputum, and upper-respiratory-tract secretions in the 28 patients with chronic bronchitis.

Non-pathogens—neisseriæ, viridans streptococci, diphtheroids, coagulase-negative staphylococci, and non-hæmolytic streptococci—were frequently found in sputum

TABLE III—POTENTIAL PATHOGENS IN MOUTHS, THROATS, AND NOSES OF 42 PATIENTS (14 " NORMALS " AND 28 CHRONIC BRONCHITICS)

Specimens		*H. infl.*	Pneumo.	Coag. + staph.	Hæm. strep.	Colif.
Site	No.					
Mouth	42	11	16	2	12	3
Throat	42	4	17	2	12	5
Nose ..	42	3	2	8	2	6

and upper-respiratory-tract secretions of both " normals " and bronchitics; they were also occasionally found in bronchial swabs from bronchitics but never in the bronchial swabs from " normals ". In 3 of the 28 bronchitics, *H. influenzæ* was recovered from sputum but not from upper or lower respiratory-tract secretions; and in a further 3, *H. influenzæ* was grown from bronchial swabs but not from sputum.

Table III shows the distribution of potential pathogens in throat swabs, saliva, and nasal swabs in the " normal " and bronchitic subjects.

Discussion

The complete absence of organisms in bronchial swabs from the 14 patients with minimal pulmonary tuberculosis (" normals ") is good evidence that the technique employed prevented contamination of the swabs with upper-respiratory-tract secretions; on the other hand, the presence of pathogens in the swabs from 23 of the 28 bronchitics suggests that organisms were being recovered from the lower respiratory tract with reasonable efficiency when they were present.

H. influenzæ and the pneumococcus were isolated jointly or severally from bronchial swabs in 21 (75%) of 28 patients with chronic bronchitis, thus confirming their close association with this condition (Mulder 1938, 1940, 1956, Mulder et al. 1952, Elmes et al. 1953, May 1953a and b, 1954, Allibone et al. 1956, Brumfitt et al. 1957). *H. influenzæ* was found more frequently than the pneumococcus in the lower respiratory tract: it was present in 15 (54%) cases; the pneumococcus was present in 9 (32%) cases; and the organisms were present together in 3 (11%) cases. Other potential pathogens were seldom isolated from the bronchial swabs of bronchitic patients; the least infrequent were members of the coliform group, which were found in 3 (11%) cases.

The pathogens found in the lower respiratory passages of the bronchitics were also found in the upper respiratory passages of " normals " and bronchitics: *H. influenzæ* was found in 4 (29%) of the " normals " and in 10 (36%) of the bronchitics; the pneumococcus in 10 (71%) of the " normals " and in 15 (54%) of the bronchitics; and coliforms in 3 (21%) of the " normals " and in 5 (18%) of the bronchitics.

These findings suggest that pathogens in sputum are often derived from the upper respiratory passages: *H. influenzæ* was cultured from sputum in 4 (29%), the pneumococcus from sputum in 8 (58%), and coliforms from sputum in 2 (15%) " normal " subjects despite the fact that these organisms were not recovered from bronchial swabs.

In the bronchitic subjects *H. influenzæ* was isolated more frequently from bronchial swabs than from upper-respiratory-tract secretions, whereas the reverse was true for the pneumococcus and other pathogens. Possibly in these chronic bronchitics *H. influenzæ* was flourishing in the bronchi when it was absent from the upper respiratory passages; or perhaps, less probably, on culture of upper-respiratory-tract secretions *H. influenzæ* was sometimes overgrown by sturdier organisms and was actually present more often than the figures suggest.

On 3 occasions *H. influenzæ* was recovered from sputum but not from upper or lower respiratory-tract secretions, this may be explained on the basis either that sampling of lower-respiratory-tract secretions by bronchial swabbing was inadequate or that the sputum was contaminated with *H. influenzæ* present in upper-respiratory-tract secretions but not isolated from them. On 3 other occasions *H. influenzæ* was grown from bronchial swabs but not from sputum: failure to culture the organism from sputum was here probably due to inadequate sampling despite the greatest care in choosing suitable specimens.

These findings accord closely with those of Brumfitt et al. (1957), who conducted a similar investigation, and confirm their conclusion that, because of contamination with upper-respiratory-tract secretions, the bacteriology of sputum may be a misleading guide to the bacteriology of the lower respiratory tract.

If it is desired to establish the relative prevalence of pathogens in the lower respiratory tract in different conditions and bronchial swabbing is not feasible, Brumfitt and Willoughby (1958) have suggested that it may be useful to culture throat swabs as well as sputum, on the ground that if an organism is recovered from sputum but not from the throat swab it may be assumed that its source is in the lower respiratory tract, though not if it is recovered from both sputum and throat swab.

This procedure, applied to the cases studied in this investigation, would have indicated that *H. influenzæ* is sometimes present in the lower respiratory tract of chronic bronchitics but never in the lower respiratory tract of " normal " subjects, because only in chronic bronchitics was *H. influenzæ* present in sputum and not in throat swabs. But it would not have indicated that other pathogens, including the pneumococcus, were sometimes present in the lower respiratory tract of bronchitics, because these organisms were all more frequently found in throat swabs than in sputum.

It will be observed from table III that *H. influenzæ*, unlike the other pathogens, was more often found in saliva than in throat swabs. When comparing the incidence of *H. influenzæ* in sputum and upper respiratory passages, it would, therefore, appear advisable to culture specimens from the mouth as well as from the throat.

As far as the clinical management of chronic bronchitis is concerned, the results of the present investigation suggest that routine bacteriological examination of sputum or of sputum and upper-respiratory-tract secretions is of little practical value. If there is evidence of infection, it would seem reasonable to base antibiotic therapy on the assumption that *H. influenzæ* or the pneumococcus—probably the former—is responsible, and to judge the efficacy of treatment by the clinical results.

Summary

Specimens of bronchial secretions, sputum, and upper-respiratory-tract secretions were obtained from 14 " normal " subjects and from 28 chronic bronchitics.

Bronchial secretions in the " normal " subjects were sterile, but in the chronic bronchitics commonly contained potential pathogens—predominantly *H. influenzæ* and the pneumococcus.

H. influenzæ and the pneumococcus were frequently found in the mouths and throats of both " normal " and chronic bronchitic subjects. These organisms were also found in sputum from " normal " subjects, and as they were not present in bronchial secretions their source must have been the upper respiratory tract.

Because of the liability to contamination with upper-respiratory-tract secretions, the bacteriology of sputum does not necessarily reflect the bacteriology of the bronchial tree: organisms can confidently be regarded as originating in the lower respiratory tract only if they cannot be cultured from the upper. But organisms in the

lower respiratory tract are so often present in the upper that culture of both sputum and oropharyngeal secretions would appear to have little practical value.

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NON-TUBERCULOUS BACTERIAL FLORA OF SPUTUM AND OF THE UPPER AND LOWER RESPIRATORY TRACT IN PULMONARY TUBERCULOSIS

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IN this country few deaths attributed to pulmonary tuberculosis are nowadays due to tuberculous toxæmia or to the progression of tuberculous lesions; the majority are due to respiratory insufficiency from bronchitis and emphysema. In some cases tuberculosis supervenes upon existing bronchitis and emphysema and does not much influence the course of events; but in many the bronchitis arises apparently as the result of bronchopulmonary damage inflicted by the tuberculosis. Because of the importance of this common sequel to pulmonary tuberculosis, it was decided to investigate the bacterial flora of the respiratory tract in cases of pulmonary tuberculosis with and without associated bronchitis and emphysema. It was thought that it would be of especial interest to compare the findings in chronic bronchitis arising as a sequel to pulmonary tuberculosis with those reported in chronic bronchitis of unknown ætiology. The bacterial flora of the respiratory tract in 9 cases of bronchial carcinoma was also studied.

Material and Methods

48 cases of pulmonary tuberculosis and 9 cases of histologically confirmed bronchial carcinoma were investigated. Cases of pulmonary tuberculosis were selected which were suitable for inclusion in one of three groups: group A, minimal tuberculosis without bronchitis; group B, extensive pulmonary tuberculosis without significant bronchitis; and group C, extensive pulmonary tuberculosis with chronic bronchitis. There were 16 cases in each of these groups.

In *group-A cases* the tuberculous lesions were small and non-cavitatory, and were responding satisfactorily to treatment with isoniazid and *p*-aminosalicylic acid (P.A.S.); there was no present evidence of bronchitis or past history of it; and patients were symptomless although they could, like many normal subjects, bring up a little sputum in the morning.

In *group-B cases* the tuberculous disease extensively involved at least three of the six lung zones; its known duration varied from six months to fifteen years, and it was being treated or re-treated with isoniazid and P.A.S. In none of these cases was there a history suggestive of bronchospasm, and there was no present evidence of obstruction to expiratory air-flow such as wheezing or subnormal performance of timed vital-capacity tests. Sputum production varied from a trifle in the morning to 15 ml. in twenty-four hours; therefore, although bronchospasm was absent, mild bronchial infection might have been present in some.

In *group-C cases* pulmonary tuberculosis involved three or more lung zones and its known duration was at least five years. In some cases the tuberculosis was active and under treatment with isoniazid and P.A.S.; in others it was inactive, and the patient had been admitted to hospital on account of chronic bronchitis. Chronic bronchitis was present in all these cases, and in all it had developed after the onset of pulmonary tuberculosis. The diagnosis of chronic bronchitis was based on a history of persistent or intermittent cough, sputum production, and dyspnœa of at least three years' duration; obstruction to the expiratory air-flow evidenced by wheezing and subnormal performance of timed vital-capacity tests; and the apparent absence of any cause of dyspnœa other than the impairment of pulmonary function.

On the morning of examination a specimen of sputum, a nasal swab, a throat swab, and a specimen of saliva were obtained from each patient. In order to sample lower-respiratory-tract secretions, a bronchial swab was next obtained, using a special technique to prevent contamination of the swab by mouth and throat secretions adhering to the end of the bronchoscope (Lees and McNaught 1959).

Results

Table I shows the distribution of potential pathogens in bronchial swabs, sputum, and upper-respiratory-tract secretions in the 16 patients with minimal pulmonary tuberculosis but without bronchitis (group A). Potential pathogens, though commonly recovered from sputum and from upper-respiratory-tract secretions, were never recovered from bronchial swabs. It is not proposed to report in detail the distribution of non-pathogens—neisseria, viridans streptococci, diphtheroids, coagulase-negative staphylococci, and non-hæmolytic streptococci—but it is noteworthy that they were never recovered from bronchial swabs in group-A patients.

TABLE I—POTENTIAL PATHOGENS IN 16 PATIENTS WITH MINIMAL PULMONARY TUBERCULOSIS BUT WITHOUT BRONCHITIS (GROUP A)

Specimens		No. in which potential pathogens were isolated					
Nature	No.	Any pathogen	*H. infl.*	Pneumo.	Coag.+ staph.	Hæm. strep.	Colif.
Bronchial swab	16	0	0	0	0	0	0
Sputum	16	12	4	8	0	8	2
Upper resp. tract	16	14	4	10	4	8	3

Table II shows the distribution of potential pathogens in specimens from the 16 patients with extensive pulmonary tuberculosis but without bronchitis (group B). Potential pathogens were found in 2 instances—*Hæmophilus influenzæ* in 1 and the pneumococcus in the other. An anomalous finding will be noted—*H. influenzæ* was found in 4 instances in sputum, once in a bronchial swab,

TABLE II—POTENTIAL PATHOGENS IN 16 PATIENTS WITH EXTENSIVE PULMONARY TUBERCULOSIS BUT WITHOUT SIGNIFICANT BRONCHITIS (GROUP B)

Specimens		No. in which potential pathogens were isolated					
Nature	No.	Any pathogen	*H. infl.*	Pneumo.	Coag.+ staph.	Hæm. strep.	Colif.
Bronchial swab	16	2	1	1	0	0	0
Sputum	16	12	4	5	1	5	2
Upper resp. tract	16	13	1	10	2	5	3

TABLE III—POTENTIAL PATHOGENS IN 16 PATIENTS WITH EXTENSIVE PULMONARY TUBERCULOSIS AND WITH CHRONIC BRONCHITIS (GROUP C)

Specimens		No. in which potential pathogens were isolated					
Nature	No.	Any pathogen	*H. infl.*	Pneumo.	Coag. + staph.	Hæm. strep.	Colif.
Bronchial swab	16	12	8	6	1	0	0
Sputum	16	15	11	8	2	2	1
Upper resp. tract	16	16	7	12	3	2	2

and once in upper-respiratory-tract secretions. On 2 occasions, therefore, *H. influenzæ* was possibly missed either in bronchial secretions from inadequate sampling or in upper-respiratory-tract secretions from overgrowth by other organisms.

Table III shows the distribution of potential pathogens in specimens from the 16 patients with extensive pulmonary tuberculosis and chronic bronchitis (group C). Potential pathogens were found in bronchial swabs in 12 (75%) cases, and in all instances but 1 the organisms were hæmophili or pneumococci.

Table IV shows the distribution of potential pathogens in the specimens from 9 patients with bronchial carcinoma. Potential pathogens were found in bronchial swabs from 6 cases, and the same organisms were also found in upper-respiratory-tract secretions of these cases. Hæmophili and pneumococci were the predominant organisms in bronchial swabs.

Table V shows the distribution of potential pathogens in specimens from the mouths, throats, and noses of the 57 patients in the series. *H. influenzæ* was more commonly recovered from saliva than from throat swabs, and the reverse was true for hæmolytic streptococci. The pneumococcus was recovered with equal frequency from mouth and throat. Except for coagulase-positive staphylococci and coliforms, potential pathogens were relatively infrequently found in the nose.

TABLE IV—POTENTIAL PATHOGENS IN 9 PATIENTS WITH BRONCHIAL CARCINOMA

Specimens		No. in which potential pathogens were isolated					
Nature	No.	Any pathogen	*H. infl.*	Pneumo.	Coag. + staph.	Hæm. strep.	Colif.
Bronchial swab	9	6	3	3	0	1	2
Sputum	9	9	3	7	1	5	3
Upper resp. tract	9	9	4	8	3	7	5

Discussion

In the 16 cases of minimal pulmonary tuberculosis (group A) organisms were never recovered from the lower respiratory tract; this was expected in view of the fact that the patients had no evidence of bronchial disease. The fact that in these cases organisms were absent in bronchial swabs despite their frequent presence in the mouth and throat indicates that the technique employed to prevent contamination of swabs with upper-respiratory secretions was effective.

TABLE V—POTENTIAL PATHOGENS IN UPPER RESPIRATORY PASSAGES OF 57 PATIENTS WITH PULMONARY TUBERCULOSIS OR BRONCHIAL CARCINOMA

Specimens		*H. infl.*	Pneumo.	Coag. + staph.	Hæm. strep.	Colif.
Site	No.					
Mouth	57	13	29	4	12	5
Throat	57	6	30	4	17	7
Nose	57	2	4	12	3	9

Potential pathogens were recovered from the lower respiratory tract in only 2 of the 16 cases with extensive pulmonary tuberculosis but without significant bronchitis (group B). In 1 case the organism was *H. influenzæ* and in the other the pneumococcus.

In the group with extensive pulmonary tuberculosis and with pronounced evidence of chronic bronchitis (group C) pathogens were present in bronchial swabs from 12 (75%) of the 16 cases. *H. influenzæ* and the pneumococcus were jointly or severally present in each of these 12 cases; a coagulase-positive staphylococcus was also found in 1. *H. influenzæ* occurred more often than the pneumococcus—in 8 (50%) cases as against 6 (37%). Many workers (Mulder 1938, 1940, 1956, Mulder et al. 1952, Elmes et al. 1953, May 1953a and b, 1954, Allibone et al. 1956, Brumfitt et al. 1957, Brumfitt and Willoughby 1958, Lees and McNaught 1959) have reported that *H. influenzæ* and the pneumococcus are by far the commonest pathogens in chronic bronchitis of unknown ætiology, and this investigation suggests that they occupy the same dominant position in chronic bronchitis arising as a sequel to pulmonary tuberculosis.

H. influenzæ and the pneumococcus were again the pathogens most often found in the lower respiratory tract of the 9 patients with bronchial carcinoma: they were each present in 3 (33%) and were present jointly or severally in 5 (55%).

H. influenzæ and the pneumococcus were present in the upper respiratory passages of a sizeable proportion of the 16 "normal" subjects in this study. *H. influenzæ* was found in the upper respiratory passages of 4 (25%), and the pneumococcus in the upper respiratory passages of 8 (50%). Of the total 57 cases in the series, *H. influenzæ* was present in the upper respiratory passages in 16 (28%) and the pneumococcus in 40 (70%).

It is generally believed that during sleep when the larynx is off-guard, and in the course of upper-respiratory-tract infections, material from the upper respiratory passages gravitates into the bronchial tree. When the bronchial tree is healthy, it will usually be able to rid itself of this infected material, but if it is extensively damaged and distorted as a result of pulmonary tuberculosis it will have less ability to do so. In these circumstances, potential pathogens from the upper respiratory tract may well be able to secure a permanent foothold in the lower respiratory tract, and it would appear that *H. influenzæ* and the pneumococcus are the ones most likely to do so. The fact that in the lung-cancer cases studied here potential pathogens isolated from the throat and mouth were also isolated from the lower respiratory tract suggests that colonisation of the bronchial tree by potential pathogens from the upper respiratory passages is liable to follow any obstructive lesion. Reid (1958) considers that in chronic bronchitis of unknown ætiology hypersecretion of mucus is the fundamental lesion; and, if this is so, here too infection may be due to an impaired ability of the bronchial tree to rid itself of potential pathogens derived from the upper respiratory tract and commonly present in it.

Sputum production and increasing dyspnœa in patients with chronic pulmonary tuberculosis are sometimes attributed, as a matter of course, to the continuing erosions of the tubercle bacillus: this investigation suggests that they may, in fact, often be due to infection caused by the same organisms as are present in chronic bronchitis of unknown ætiology—predominantly *H. influenzæ* and the pneumococcus. In non-tuberculous chronic bronchitis

and in bronchiectasis short-term and long-term antibiotic regimes have proved of great value, and there is little doubt that the same treatment might be employed with benefit more often than it is in chronic pulmonary tuberculosis.

Comparison of the results of bacteriological examination of sputum and upper-respiratory-tract secretions in this investigation shows that examination of sputum is unlikely to help in the choice of antibiotic: potential pathogens cultured from sputum may derive from the lower respiratory tract, but on the other hand they may derive from the mouth or throat. Sputum examination would have been a misleading guide to the bacteriology of the bronchial tree in the 16 cases with minimal pulmonary tuberculosis (group A); table I shows that although pathogens, particularly the pneumococcus and *H. influenzæ*, were often isolated from sputum, their source was the upper, not the lower, respiratory tract. If upper-respiratory-tract secretions were examined as well as sputum, potential pathogens which were found only in sputum could be presumed to come from the lower respiratory tract, but if the organisms were found both in upper-respiratory-tract secretions and in sputum, their source would be uncertain (Brumfitt and Willoughby 1958). Table IV, which shows the distribution of potential pathogens in the nose, mouth, and throat, suggests that culture of a throat swab would give a fair indication of the organisms in the upper respiratory passages likely to contaminate sputum except for *H. influenzæ*, which was found in throat swabs less often than in specimens of saliva. Comparison of the bacteriology of sputum with that of throat swabs and saliva is, however, tedious and uncertain, and bronchial swabbing is not practical for routine work. In the clinical management of pulmonary tuberculosis with bronchitis, it would therefore seem best of dispense with routine bacteriology as a guide to therapy and to select an antibiotic such as tetracycline effective against both the important pathogens —*H. influenzæ* and the pneumococcus.

If, as seems probable, potential pathogens of the mouth and throat are particularly liable to colonise an already damaged bronchial tree, patients with lungs extensively affected by tuberculosis are at risk. It is therefore suggested that, in the supervision of these patients, bronchopulmonary infections should be treated promptly and efficiently and that the utmost vigilance should be exercised in preventing the downward extension of upper-respiratory-tract infections.

Summary

Specimens of bronchial swabs, sputum, and upper-respiratory-tract secretions from 16 patients with asymptomatic minimal pulmonary tuberculosis, from 16 patients with extensive pulmonary tuberculosis without significant bronchitis, from 16 patients with extensive pulmonary tuberculosis and chronic bronchitis, and from 9 patients with bronchial carcinoma were obtained and cultured.

Bronchial secretions from the asymptomatic minimal cases were sterile; but potential pathogens, predominantly *H. influenzæ* and the pneumococcus, were commonly cultured from the bronchial secretions of the patients with tuberculosis and chronic bronchitis. Potential pathogens (*H. influenzæ* and the pneumococcus) were cultured from bronchial secretions in only 2 of 16 patients with extensive pulmonary tuberculosis but without significant bronchitis. Potential pathogens, predominantly *H. influenzæ* and the pneumococcus, were commonly cultured from bronchial secretions in the patients with bronchial carcinoma.

The potential pathogens found in the bronchial secretions of patients with bronchial disease were often present in the upper respiratory passages and in the sputum of patients in all groups.

The bacteriology of sputum is not a reliable guide to the bacteriology of the bronchial tree, as pathogens cultured from it may be derived from the upper, not the lower, respiratory tract.

It is suggested that potential pathogens in the upper respiratory tract are liable to colonise a damaged bronchial tree; in patients who have had extensive pulmonary tuberculosis episodes of bronchial infection should, therefore, be treated early and vigorously.

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THE SPINAL BRUIT

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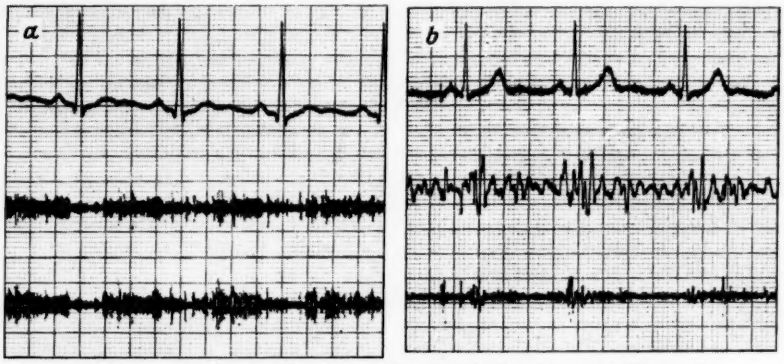
THE value of the cranial bruit in the diagnosis of cerebral vascular abnormalities is well recognised, but remarkably little attention has been paid to the possibility of a comparable spinal bruit. Because cases of spinal angioma are reported under many headings, published accounts are difficult to trace, but I have not found a spinal bruit described. Moreover, the possibility is not generally appreciated, because recent detailed accounts of spinal angiomata do not mention auscultation as a routine procedure (Girard and Garde 1955, Newman 1959).

De Jong's (1950) exhaustive work on neurological examination recommended inspection, palpation, percussion, and auscultation of the skull, but stopped short at percussion of the spine. Wyburn-Mason (1943) listened over the spine in ten cases of spinal angioma, although he mentioned auscultation specifically only in four case-histories where the results were negative. The only example of spinal auscultation in this condition recorded previously was that of Ford (1937), which was negative also. Henson and Croft (1956) heard no bruit in their cases of spontaneous spinal subarachnoid hæmorrhage, nor did Lake (1957) over a vertebral angioma.

It seems, therefore, that this sign may not have been reported previously; certainly it has been sought very seldom, and attention might usefully be drawn to this simple diagnostic aid.

Case-reports

Case 1.—This boy, aged 17, was admitted urgently to the Derby City Hospital in November, 1955, with intense headache and photophobia. Pain had started suddenly that morning; he later remembered that it struck in the middle of the dorsal spine, but rapidly moved to the head and neck. He showed gross neck rigidity, but Kernig's sign was negative. The right leg was generally thinner than the left, and was weak and spastic; this was said to date from his being knocked down by a car at the age of 10 years, since when he had walked with a slight limp. The other limbs were normal; sensation was intact; and speech was unaffected. He had dorsal scoliosis.



Postoperative phonocardiograms of the spinal bruits: (*a*) case 1; (*b*) case 2.

Lumbar puncture revealed heavily bloodstained cerebrospinal fluid (C.S.F.) under high pressure. Severe headache and neck retraction continued, and the boy became confused and drowsy. At this stage I thought the spastic and ill-developed leg might be the result of a left hemisphere angioma; and Mr. Clark Maxwell performed left carotid angiography 7 days after the hæmorrhage, with normal findings. 5 days later diplopia appeared, and was found to be due to a left sixth-nerve palsy.

The patient's condition improved steadily. He was discharged from hospital in January, 1956, free from headache and diplopia, and he returned to work. In December he noticed more weakness of the right leg and soon the left became weak also. The weakness increased gradually, but there was no pain or evidence of further bleeding. He was readmitted to hospital in May, 1957, when he had moderately severe spastic paraparesis but he could just walk with assistance. The right leg was the more severely affected, the thigh being 5 cm. and the calf 2·5 cm. less in circumference than on the left. The tendon reflexes were exaggerated and both plantar responses were extensor. All forms of sensation were impaired below the T8 segment.

Somewhat belatedly thinking of a spinal angioma, I listened over the spine. I heard a loud bruit over the T7–9 vertebræ, which was audible for about 4 cm. to either side, and louder on the left. No pulse or thrill was palpable over the spine, but the bruit was rhythmic, correlating with the apex-beat.

At lumbar puncture the pressure was 160 mm. of water, with no rise on jugular compression. The C.S.F. contained 55 mg. of protein per 100 ml., and 7 lymphocytes per c.mm. Radiographs of the spine showed dorsal scoliosis with the lower curve convex to the left. Both pedicles of the T8 and 9 vertebræ, and those on the left of the T5–7 vertebræ, were flattened. Lumbar myelography showed a block at the lower border of T9, with large filling defects due to dilated vessels as low as T12. Cisternal myelography showed another block at the upper border of T8 with evidence of abnormal vessels as high as T1.

The patient was transferred to the Sheffield Royal Infirmary under the care of Mr. Antony Jefferson, who decided, in view of the advancing paraplegia and spinal block, that decompression and exploration were indicated. He removed the laminæ of the T6–10 vertebræ, without finding undue vascular tissue superficially. But on opening the dura a mass of reddish vessels was seen within and expanding the spinal cord. Above the expanded portion enlarged vessels appeared on the surface. No direct operative attack on the tumour was considered feasible.

The paraplegia progressed further, and when the patient was last seen in March, 1959, both legs were totally paralysed and spastic. Sensation was impaired at and below the T6 segment. He had no voluntary sphincter control. The bruit was even louder, no doubt owing to removal of the laminæ, being an almost continuous high-pitched murmur with regular accentuation (see figure a).

Case 2.—Mr. R. H. Shephard kindly allowed me to examine this girl, who was under his care. As he intends to publish the case in another context, I shall not give full clinical details.

The patient had had a proven subarachnoid hæmorrhage in February, 1956, at the age of 10, and a year later the findings at bilateral carotid angiography were normal. In November, 1958, she began to have pain in the back and both legs, and paraparesis, which increased rapidly, without evidence of further hæmorrhage. When admitted to the Derbyshire Royal Infirmary a severe cauda-equina lesion was evident clinically. As she was in great pain, which was aggravated by movement, my personal examination was limited to listening over the spine. I heard a loud bruit maximal over the T12 and L1 vetebral spines, but audible for about 5 cm. around this area.

The diagnosis of spinal angioma was confirmed radiologically. Mr. Shephard performed a laminectomy at the T10 to L1 level, and found an intradural angioma, its large vessels containing both arterial and venous blood. He was able to remove much of the tumour, which lay posteriorly, with great benefit to the patient. At first the operation seemed to have stopped the bruit, but a much softer sound is now audible over the centre of the laminectomy scar (see figure b).

Discussion

The discovery of a bruit over a spinal angioma is hardly surprising. In these two cases it was apparently produced in the angioma itself or the feeding vessels, the tissues posterior to the spine being not unduly vascular. The sign is by no means invariably present; it was not heard by Ford (1937), Wyburn-Mason (1943), or Henson and Croft (1956), nor in a further case which I examined, even after laminectomy. In the cases reported here the cause of the bruit is uncertain, but both tumours had a large arterial element and had caused a spinal block; and these are uncommon features of angiomata.

Spinal angiomata are often difficult to diagnose, whether they present with subarachnoid hæmorrhage or with spinal-cord symptoms. In these two cases the bruit merely confirmed the diagnosis, but both patients had been investigated previously for supposed intracranial subarachnoid hæmorrhage at a time when the bruit may have been already present. Each bruit was later loud and unmistakable. These experiences suggest that a few minutes spent in listening over the spine may occasionally elucidate a problem of unexplained subarachnoid hæmorrhage or spinal cord symptoms.

Summary

A bruit was heard over the lesion in two cases of intradural spinal angioma.

This sign, which probably has been sought seldom, is likely to be of occasional diagnostic value.

I am indebted to Mr. Antony Jefferson for permission to publish his operative findings in case 1, and to Mr. R. H. Shephard for permission to examine and report on case 2.

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EVENING COLIC IN INFANTS

A DOUBLE-BLIND TRIAL OF DICYCLOMINE HYDROCHLORIDE

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EVENING colic, also termed " three months' colic ", is an annoying condition in healthy thriving babies in the first three months of their life; and not one of innumerable different methods of treatment recommended has proved satisfactory. I reviewed elsewhere published reports concerning evening colic (Illingworth 1954). A blind trial of methyl scopolamine nitrate (' Skopyl ') (Illingworth 1955) indicated that this drug was useless in the dosage employed, the control inert substance giving just as much or more relief than the active drug. It seemed possible that an anticholinergic drug might be useful, and accordingly I decided to conduct a double-blind trial of dicyclomine hydrochloride (' Merbentyl ', diethylaminocarbethoxybicyclohexyl hydrochloride). This acts as a parasympathetic depressor, and has very few side-effects.

Pakula (1952) tried this drug in infantile colic, and was convinced of its value.

Method of Study

The study was carried out in the well-baby clinic at the Jessop Hospital, Sheffield. The diagnosis was based on rhythmical attacks of screaming in the evenings in well, thriving babies who were gaining not less than 7 oz. per week during the period of observation. An important condition for admission to the study was the mother's statement that the screaming continued unabated when the baby was picked up. All the babies were seen by me. All babies were less than 8 weeks old when treatment was instituted.

When I was satisfied with the diagnosis I prescribed dicyclomine; and the pharmacist then dispensed either dicyclomine or an inert substance by random sampling. I saw the child a week later and recorded the mother's words about the colic. The medicine was prescribed again, and the pharmacist then gave the opposite of that which she had given before—e.g., the active drug if the control material had been given on the first occasion. I saw the child again a week later. Only the pharmacist knew which material the child received. Only when I had tabulated all my results was I given the code which indicated the treatment given on each occasion.

The results were graded from −3 to +3. +1 signified that the child was slightly better, +2 that he was definitely better but still had some discomfort, +3 that he was very greatly improved and free from symptoms. −1 meant that he was slightly worse. A total of 20 patients were studied, but unfortunately 4 did not have the inert substance and 1 did not have the active drug.

The dosage used was half a teaspoonful (approximately 5 mg.) before the 6 P.M. feed.

Results

Of 16 patients receiving the inert substance 8 were unaffected, and the remaining 8 were given a total score of +19, 4 patients receiving +3 each. The mean score was +1·18 (see table).

Of 20 patients receiving the active drug, 1 was unaffected, the remaining 19 patients being given a total score of +47. 12 patients were given +3 each. The mean score was +2·35. No patient in either group was worse with the treatment, unlike patients in the methylscopolamine-nitrate study referred to above.

3 mothers found the inert substance more effective than the active drug, 2 of these differing by one point: the total difference was +5. 9 mothers found the active substance better than the inert one, the total difference being 20.

Typical remarks were as follows:

" The second bottle didn't have the same effect as the first." (First was active.)

" The first bottle was better." (First active.)

" The first bottle was no use. He improved greatly on the second." (Second active.)

" The first bottle didn't help. The second worked wonders." (Second active.)

" The first made no difference. The second bottle stopped the colic." (Second active.)

Nevertheless a single mother spoke in glowing terms of both bottles, saying that " it was like magic ", and had " done him the world of good ". A mother of a baby who received the active drug alone said that he was " much, much better. I'm so much relieved. The improvement was immediate ".

SCORES ALLOTTED IN DICYCLOMINE STUDY

Case no.	End of first week	End of second week
1	*+2*	0
2	*+3*	*+3*
3	+3	*+3*
4	*+2*	0
5	0	*+3*
6	+3	*+3*
7	0	*+3*
8	*0*	+3
9	*+1*	0
10	*+3*	+2
11	*+3*	Defaulted
12	0	*+3*
13	*+1*	+2
14	+3	*+2*
15	0	*+3*
16	*+1*	+1
17	*+2*	0
18	+2	Defaulted
19	*+3*	Defaulted
20	*+3*	Defaulted

Italic figures are scores obtained on the active drug.

Discussion

Evening colic is a self-limiting condition, curing itself by the age of 2 months in mild forms, and by 3–4 months in severe forms. In a trial of a drug for such a condition, the double-blind method is very satisfactory; for, each patient being his own control, the factor of the increasing age of the child should be eliminated. The table shows that the factor of the increasing age of the child has not affected the results. Mothers are great believers in the magic of medicine, and the double-blind method effectively disposes of this factor in the assessment of results. Several mothers were strikingly dogmatic about the difference in the effect of one bottle from that of the other; and in 7 out of 8 of such cases the mother's opinion that one of the two bottles was ineffective corresponded to the fact that the offending bottle contained an inert substance.

In the methyl-scopolamine-nitrate trial (Illingworth 1955) random sampling was used, but not the double-blind method. In that study 20 control babies received the inert substance, and 20 received the active drug. 14 in the " active group " were helped by the drug, and 5 were made worse: 16 were helped by the inert substance, but none were made worse.

A further striking fact has emerged from the present study—the decline in the number of babies suffering from evening colic. I cannot explain this. The feeding habits of the babies in the past two years do not appear to be any different from those in previous years. The clinical picture is so striking that there cannot have been any error of diagnosis in either group. Whereas five to ten years ago I frequently saw severe cases of evening colic, I rarely see such cases now.

Summary

A double-blind study of the effect of dicyclomine hydrochloride (' Merbentyl ') on evening colic in infants (" three months' colic ") has proved that the drug is of considerable value. No other drug has been proved to be of value in the treatment of this condition.

I wish to thank Riker Laboratories Ltd., Loughborough, for supplying the dicyclomine and the inert material as control; and Miss C. Wood, chief pharmacist at the Jessop Hospital, Sheffield, for her cooperation. Dicyclomine is now marketed by Merrell National (Laboratories) Limited.

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PREDNISONE IN THE RELIEF OF ACROPARÆSTHESIÆ

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IN a recent review of 150 cases of acroparæsthesiæ, the results of which are to be published later, we came to the conclusion, previously reached by others (Brain et al. 1947, Kremer et al. 1953, Garland et al. 1957, Heathfield 1957), that carpal-tunnel decompression almost always cures this condition. On the whole, medical treatment has been disappointing, and we have failed with tolazoline (' Priscol '), nicotinic acid, and various other putative vasodilator drugs. But if a suitable medical remedy could be evolved it would have definite advantages in certain circumstances—e.g., if there was any doubt about the diagnosis; as a temporary form of treatment whilst awaiting operation; if operation was contraindicated or if the patient (as often happens) expressed a wish not to have an operation; and in certain patients with associated diseases, particularly rheumatoid arthritis affecting the hands. During this investigation we observed with interest that arthropathy might be present in patients who complained of typical acroparæsthesiæ. The association is shown in the following examples.

Case-reports

Case 1.—In February, 1958, a woman of 52 complained of pins and needles in both hands. This awakened her in the early hours of the morning, and she had similar sensations occasionally when carrying a shopping-bag or when gripping. The index and middle fingers were affected mainly, and the trouble lasted about 15–20 minutes, usually being relieved by arm movement. From time to time she complained also of pains in her neck, and of aching in the finger-joints, wrists, and ankles.

In June, in the Department of Surgery, cervical spondylosis was diagnosed because radiographs of the cervical spine showed narrowing and osteophyte formation at the c5/6 disc space. In September, when she was seen in the Department of Neurology, her symptoms were unchanged but she had swelling of the interphalangeal joints, wrists, and right ankle. The erythrocyte-sedimentation rate was 32 mm. in the 1st hour (Wintrobe), and radiographs of the wrists showed some juxta-articular porosis.

Acroparæsthesiæ with associated arthropathy was diagnosed, and although carpal-tunnel decompression was contemplated we decided to try giving her prednisone 5 mg. t.d.s., to see whether the pain in the wrists could be relieved and whether the acroparæsthesiæ would be affected. A month later she pronounced the tablets " absolutely wonderful "; all the joint swelling had gone, and she had had no further attack of paræsthesiæ. She remained very well on this dosage, and when last seen in April, 1959, she had resumed work.

Case 2.—In mid-December, 1958, a woman of 26 developed acroparæsthesiæ in both hands (the right being affected more than the left), which woke her four or five times nightly. She had some tingling in the day time too, and occasionally she had pains in her back and metacarpophalangeal joints. Because the metacarpophalangeal joints were swollen, we thought there might be an associated arthropathy. We again decided to try the effect of prednisone 5 mg. t.d.s. Her symptoms had improved considerably after a week, and this improvement has been maintained. In April, 1959, prednisone was discontinued and the trouble recurred. When prednisone was given again the acroparæsthesiæ disappeared, though she still complains of a little pain in the metacarpophalangeal joints.

Because of the symptomatic success in these 2 cases we decided to extend the use of prednisone to others in which no arthropathy could be demonstrated. 2 other patients with arthropathy have been so treated with improvement in both the paræsthesiæ and arthropathy, but we have also treated 13 patients with acroparæsthesiæ but without arthropathy. All the results are summarised in the table.

Case 3 provides another characteristic history. In October, 1958, a woman of 51 began to get typical acroparæsthesiæ in both hands, which usually woke her in the early hours of the morning, sometimes two or three times, and came on occasionally during the day when she rested and when knitting. The interphalangeal joints showed slight spindling, but neurologically there were no abnormal findings. We decided to try the effect

SUMMARY OF CASES OF ACROPARÆSTHESIÆ TREATED WITH PREDNISONE (ALL WERE FEMALE)

	Case no.	Age (yr.)	Duration of acroparæsthesiæ	Response to prednisone	Side-effects	Duration of therapy to date (wk.)	Effect of discontinuing therapy
Arthropathic group:	1	52	6 mos.	Complete relief	Nil	24	
	2	26	6 wk.	Almost complete relief	Nil	20	Recurrence of acroparæsthesiæ
	3	51	5 mos.	Immediate complete relief	Nil	8	Mild recurrence after 10 days
	4	51	2 yr.	Immediate relief	Nil	4	
Non-arthropathic group:	5	42	11 mos.	Immediate complete relief	Nil	4	
	6	42	7 yr.	Complete relief	Gastrointestinal symptoms	6	Acroparæsthesiæ recurred; patient wanted operation
	7	47	27 „	Immediate complete relief	Nil	4	
	8	38	11 „	Relief not quite complete	Nil	4	
	9	57	6 mos.	Little effect	Gastrointestinal symptoms	4	
	10	51	1 yr.	Much improved	Œdema of face	4	Symptoms returned
	11	44	18 mos.	Complete relief	Nil	6	
	12	62	10 yr.	„ „	Nil	6	
	13	29	6 mos.	Much improved	Nil	4	
	14	42	7 yr. (left) 3 „ (right)	Partial relief	Nil		
	15	31	6 yr.	Immediate complete relief	Nil	8	
	16	48	14 „	„ „ „	Nil	4	
	17	52	7 mos.	Much improved	Nil	4	

of prednisone. This gave her immediate and complete relief for about 6 weeks. She then became aware of "a sense of stiffness" in the head, and, because she imagined this was due to prednisone, she stopped the treatment. But after 10 days the acroparæsthesiæ returned, and she took prednisone again without further adverse effect. When last seen on June 19, 1959, her symptoms were completely controlled by prednisone.

Cases 4 and 5 (see table) had immediate and complete relief from prednisone, and they have continued the course of treatment prescribed. Case 4, who had been advised to have an operation, has now refused this temporarily because the medical treatment has been so effective.

Case 6 is noteworthy. She was a woman of 42, who began to have acroparæsthesiæ affecting mainly her index and ring fingers in March, 1952. Her symptoms became much worse in 1957, and when seen in March, 1959, she was exhausted because she could not sleep; she noticed the trouble also in the day time whenever she was resting. In the clinic we advised her to have a carpal-tunnel decompression, but as a temporary measure she was given prednisone. This stopped the attacks of paræsthesiæ immediately, but unfortunately it was discontinued after 3 weeks because of severe indigestion. The indigestion ceased immediately, but 2 weeks later the acroparæsthesiæ came back and have returned gradually to their former intensity. Operation has been advised once more.

The points which emerge from this history are that, although adverse effects are to be expected, discontinuation of prednisone is followed by a recurrence of acroparæsthesiæ, as was noted in case 3 also.

Gastrointestinal side-effects from prednisone were encountered again in case 9, a patient who had parkinsonism in addition to atypical acroparæsthesiæ, but in this case prednisone had little effect on the acroparæsthesiæ. Cases 10 and 11 also had parkinsonism as well as acroparæsthesiæ; the significance is not clear. Although it might be fortuitous, the relative immobility of the hands may have contributed to the development of acroparæsthesiæ.

Discussion

There are undoubted advantages in having at one's disposal some medical means of alleviating troublesome acroparæsthesiæ, although in the majority of cases the definitive treatment is clearly that of carpal-tunnel decompression. We cannot yet say whether cessation of treatment after 3 or 4 months is followed by lasting benefit, but we hope to obtain more information. Meanwhile the administration of prednisone for symptomatic relief of acroparæsthesiæ pending operation seems justified by these results.

Apart from practical considerations, however, our observations on acroparæsthesiæ associated with the carpal-tunnel syndrome have given us an opportunity to make certain theoretical deductions on the possible mode of action of prednisone in this condition. It seems reasonable, in the light of our present knowledge, to suggest that there are two components of the syndrome, which may each occur independently. The immediate cause of the acroparæsthesiæ is compression of the median nerve in the carpal tunnel and beneath the carpal ligament. In certain cases, and particularly those with arthropathy, the tunnel itself may be narrowed. In others the process must be one which brings about an increase in the volume of the contents of the carpal tunnel; and we feel it is significant that in 19 of our 150 patients the condition either began or was greatly accentuated during pregnancy. This increase of carpal-tunnel volume may, of course, be due to a change in the total volume of the arm, which may take place in a normal person at rest but is likely to be greatly aggravated if there is deformity in the carpal tunnel.

Many of our patients complained of actual swelling of their hands, particularly during pregnancy; they have said that during the attack the hand feels thick or distended or "like a boxing-glove". Some patients complained that their wedding-rings had become tight, and we have observed obvious swelling of the hands during the day in a few patients, especially those who were pregnant. Shaking the arm and hand reduces the symptoms in the majority of patients with acroparæsthesiæ, since this manœuvre probably removes stagnant tissue-fluid which has collected as a result of gravity or immobility during sleep. Such movement would be unlikely to afford relief if the symptoms were due entirely to a structural lesion and not to fluid changes.

Heathfield (1957) offered two explanations. He suggested firstly that lying on the arm during sleep would cause symptoms by ischæmic compression, and secondly that œdema of the tissues, maximal during sleep, might be at least partly responsible.

It seems to us that simple arterial insufficiency during the period of immobility would not be a satisfactory explanation of the symptoms, and we favour Heathfield's second factor of tissue œdema.

Kremer et al. (1953) also stressed transient swelling of the soft tissues in the neighbourhood of the nerve as one factor precipitating attacks of acroparæsthesiæ, and suggested that their nocturnal occurrence might be related to venous obstruction, due to lying on the arm, with subsequent carbon-dioxide retention during sleep, and consequent vasodilatation and increased production of tissue-fluid.

On the whole we are disinclined to accept the idea of venous stasis though we agree that increase in the tissue-fluid, because of stasis and biochemical changes, may be the real nocturnal precipitating factor.

Taking into account the possibilities of arthropathy and abnormal tissue-fluid distribution, we gave prednisone to some of our patients. The drug clearly acted primarily on the arthropathic factor in certain patients, particularly cases 1, 2, and 3. (We later noted with interest the comments of Philip [1959].) But having extended the trial to cases without arthropathy, and having found that prednisone was almost equally effective, at least temporarily, we concluded that the usual increase in the volume of the arm at rest, particularly at night, was altered by prednisone. It seemed likely that prednisone produced its beneficial effect by causing a redistribution of body-fluid, so preventing fluid accumulation in the carpal area. The effects of corticoids on fluid distribution are complex. One is tempted to imagine that fluid retention with subsequent tissue œdema would increase the volume of the arm rather than diminish it; but the speed of action of prednisone in acroparæsthesiæ does not support this idea, and the effect of prednisone points to the reverse. We recall that Camara and Schemm (1955) showed that corticotrophin may in fact produce diuresis in cardiac failure. We can only conclude from the success of prednisone in the treatment of acroparæsthesiæ—with or without arthropathy—that the effect of corticoids is not merely to produce peripheral tissue œdema.

Summary

17 cases of acroparæsthesiæ were treated with prednisone. The dosage was 5 mg. three or four times daily.

Prednisone was initially tried in cases where acroparæsthesiæ were associated with definite arthropathy. Success encouraged the use of the same treatment in other cases without demonstrable arthropathy. Further success

led to the conclusion that the most important factor in the production of acroparæsthesiæ is the increase in the volume of the contents of the carpal tunnel.

Whether lasting benefit results from a limited course of treatment with prednisone is not yet known.

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ANAL LESIONS IN CROHN'S DISEASE

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IN patients with Crohn's disease the high incidence of anal complications, such as fissure and fistula, is well recognised. But it is less well known that many of these anal lesions appear clinically indolent and unusual, sometimes suggesting tuberculosis. Moreover, in many cases histological examination of tissue from the wall of the fissure or fistula may reveal non-caseating giant-cell systems similar to those sometimes found in the intestinal lesions of Crohn's disease.

47 patients with Crohn's disease have been seen at St. Mark's Hospital in recent years. This series is unusual because the large bowel was diseased in 25 patients, while in 22 the terminal ileum only was involved. 19 patients either had a fistula when they were first examined or gave a past history of anal fistula, and 4 had anal fissures. Anal complications were seen, therefore, in 23 of the 47 patients—the incidence of nearly 50% being higher than in any series so far reported. This figure, together with the high incidence of large-intestinal disease, probably reflects the work of this special hospital, which is concerned mainly with diseases of the colon and rectum.

Analysis of Cases

History

12 of these 23 patients with Crohn's disease gave a history of abdominal pain or disturbance of bowel function as the initial complaint, and only later in the course of the disease did an anal fissure or fistula appear. In the other 11 patients the fistula preceded or coincided with the onset of the abdominal symptoms; 5 of them gave a history of recurrent anal fistulæ, with several operations over many years, before abdominal symptoms arose.

Type of Anal Lesion

In 10 patients who had an anal lesion when first seen the clinical appearance was unusual, suggesting tuberculosis. 2 of them had one or more relatively painless anal fissures, which looked dirty and indolent, with undermined edges; the other 8 had anal fistulæ which appeared indolent and were not indurated on palpation. Of the remaining 13 patients 9 gave a history of a fistula which had either healed spontaneously or responded to surgical treatment, and they had no anal lesion when seen at this hospital. The other 4 when first seen had anal fistulæ which did not arouse suspicion of tuberculosis nor provoke comment by the clinician.

The anal fistulæ were of all types, from the very simple low-level direct type to complex fistulæ extending into the rectum above the anorectal ring. There was 1 case of rectovaginal fistula, but no example of a fistula leading from the perineum directly into an intraperitoneal viscus. In many cases more than one fistula was present at the same time, and both simple and complex fistulæ was seen in the same patient.

Rectal Examination

All the patients were examined by sigmoidoscopy, and in the majority no abnormality was found. But many of the patients with disease of the large intestine had proctitis, which varied in degree from mild œdema of the mucosa with an occasional shallow ulcer, to severe diffuse inflammation. A few patients with severe proctitis also had anal strictures which were tender, bleeding easily when examined.

Histology

Histological material was available in 12 of the 23 cases. In each, non-caseating giant-cell systems were found in granulation tissue removed from the anal lesion. These 12 cases included the 4 in which the fistulæ was not clinically suggestive of tuberculosis.

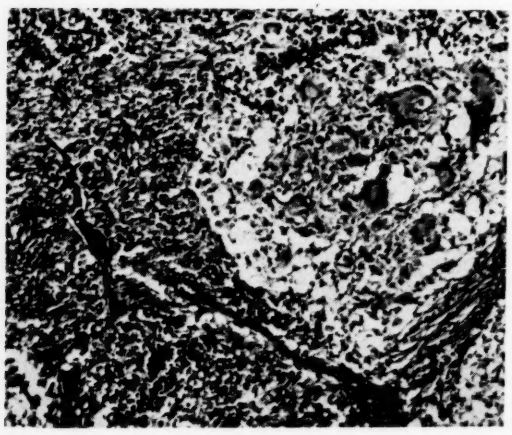

Fig. 1—Non-caseating giant-cell systems from an anal fistula, which are similar to those seen in the intestinal lesions of Crohn's disease. (Hæmatoxylin and eosin. ×80.)

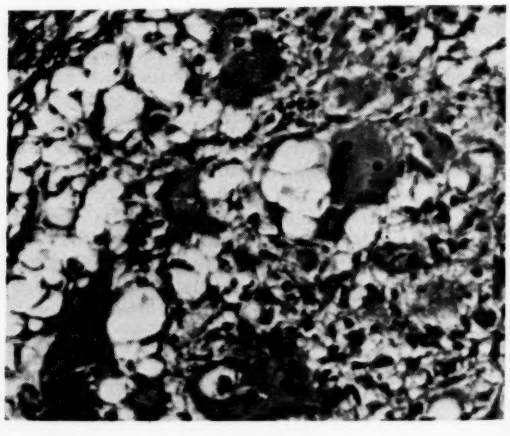

Fig. 2—High-power view of fig. 1. The giant-cell systems are composed of giant cells and epithelioid cells mixed with round cells, which are mainly lymphocytes; there is no central caseation. (Hæmatoxylin and eosin. ×400.)

The giant-cell systems of Crohn's disease (figs. 1 and 2) show one or more multinucleated giant cells lying in a network of epithelioid cells mixed with mononuclear cells, which are principally lymphocytes. Sometimes giant cells are absent, the centre of the system consisting only of epithelioid cells. The individual giant cells resemble those seen in tuberculosis, but the whole lesion is usually smaller than the typical tubercle, with no sign of central caseation. The lesions resemble sarcoid rather than tuberculosis, and they may be justifiably referred to as a " sarcoid reaction ". Except that patients with Crohn's disease never develop sarcoidosis elsewhere (such as the lungs, liver, lymph-glands, or skin), one could regard the two diseases as the same. Moreover, involvement of the gastrointestinal tract in sarcoidosis is extremely rare.

Since the work of Gabriel (1921) on the histology of fistulæ, it has been customary at St. Mark's Hospital to examine histologically pieces of tissue from most patients operated on for anal fistulæ, and a few of these have shown giant cells or giant-cell systems. Until it was recognised that the giant-cell systems often seen in the intestinal lesions of Crohn's disease might be present in the anal lesions also, fistulæ with these histological features were frequently reported as " suggestive of a tuberculous lesion " (although it was realised that a pathologist cannot diagnose tuberculosis confidently in the absence of central caseation or bacteriological confirmation). Nevertheless such a histological report, in conjunction with the indolent nature of the anal lesion on clinical examination, often led to a diagnosis of tuberculous fistula, with all its social and therapeutic implications. Some of the patients in this series who were incorrectly thought to have tuberculosis received antituberculous chemotherapy or sanatorium treatment, but this did not improve their condition.

Histologically the presence of giant cells in an anal fistula should suggest the possibility of a foreign-body reaction, tuberculosis, or Crohn's disease. But there may be other causes of giant-cell histology in anal lesions which are at present unknown. The differential histological diagnosis of giant cells in anal fistulæ may be represented diagrammatically as in fig. 3.

Discussion

The clinical appearance of the anal lesions associated with Crohn's disease may be suggestive of tuberculosis, and when giant-cell systems are found by a pathologist in biopsy material from a lesion tuberculous anal fistula will probably be diagnosed. Experience in this hospital has shown that in some patients with anal fistulæ, formerly regarded as tuberculous, a diagnosis of Crohn's disease has been later established, and we now realise the high incidence of non-caseating giant-cell systems in anal lesions associated with Crohn's disease. We believe that in this country the finding of giant-cell systems in anal fistulæ is as likely to be associated with Crohn's disease as with tuberculosis, and we would stress that a tuberculous anal fistula should not be diagnosed without clinical and bacteriological confirmation.

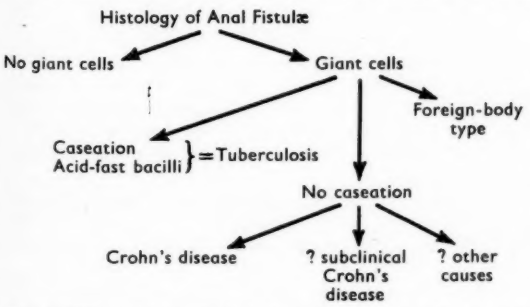

Fig. 3—Differential histological diagnosis of giant cells in anal fistulæ.

Crohn's disease, however, is not always easy to diagnose. More than once in this series, after giant-cell systems were seen in material from an anal fistula, barium-meal and follow-through examinations were made and no radiographic abnormality was found. Only after a later X-ray examination, requested when intestinal symptoms persisted or recurred, was the intestinal lesion demonstrated. In 2 cases over twelve years elapsed between the onset of an anal fistula and the firm diagnosis of Crohn's disease of the small intestine.

Several patients now under observation at this hospital are apparently well but have had anal fissures or fistulæ in which giant-cell systems were found. None of them has any clinical or bacteriological evidence of tuberculosis, nor any radiographic sign of intra-abdominal Crohn's disease. But we think that some of these patients may later prove to have intestinal Crohn's disease.

Summary

23 cases of Crohn's disease had anal fistulæ or fissures, and in 10 the clinical appearance of the anal lesions suggested tuberculosis.

Tissue from the anal lesions was examined histologically in 12 cases and found to contain non-caseating giant-cell systems similar to those in the intestinal lesions of Crohn's disease.

Thus when a pathologist finds giant-cell systems in histological material from an anal fistula, Crohn's disease should be considered in the differential diagnosis.

Our thanks are due to the surgical staff of St. Mark's Hospital for permission to study their cases, and to Dr. Cuthbert Dukes for advice in preparing this paper. The expenses of the investigation were met out of a block grant to the Research Department of St. Mark's Hospital from the board of governors of the Hammersmith and St. Mark's group of hospitals.

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RETICULAR DYSGENESIA

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THE following cases, as far as we know, are the first reported examples of reticular dysgenesia with congenital aleukia.

Report of Cases

Male twins (cases 1 and 2) were born about 6 weeks prematurely on April 20, 1958. Case 1 weighed 4 lb. 5 oz. (2·25 kg.) and was 17½ in. (45 cm.) long; case 2 weighed 3 lb. 10 oz. (1·64 kg.) and was 15 in. (39 cm.) long.

Next day, when they did not seem to be doing well, examination of the blood revealed a total absence of white blood-cells, both in the counting-chamber and in smears. The red blood-cells appeared normal: normoblasts were few, and thrombocytes were within the normal range. The hæmoglobin was 110% in both infants. Despite treatment with penicillin and γ-globulin, both children died in a septic condition, one on the 5th and the other on the 8th day.

At no time had recognisable leucocytes been seen in the peripheral blood. Thrombocytes were never absent. Although

PLASMA-PROTEIN ELECTROPHORESIS

Type of protein	Case 1		Case 2
	Before correction	After correction for fibrin and Hb	
Total (g. per 100 ml.)	5·6	4·6	8·2
Albumin (%)	46·8	51·4	44·2
α_1 globulin „	12·3	13·6	8·2
α_2 globulin „	8·5	9·3	9·8
Hb „	8·9	..	7·4
β globulin „	9·4	10·3	15·2
γ globulin „	14·1	15·4	15·2

It is not certain that the substance moving between α_2 and β was Hb. The form of the γ-globulin spot is peculiar and the borders of the fibrinogen spot are very sharp.

the prothrombin-time was distinctly prolonged on the 3rd day, no hæmorrhagic tendency was seen. The plasma-proteins were electrophoretically investigated on the 3rd day, with the results shown in the table.

On the last 3 days of life case 2 was given intravenously suspensions of leucocytes from compatible blood-donors (varying from 7000 to 40,000 leucocytes per million erythrocytes per c.mm.). Immediately after the injection a very few leucocytes could be counted. 15 minutes later no white cells could be traced. (This rapid disappearance of infused leucocytes seems to be encountered also under normal circumstances.)

Family History and Investigations

The parents were both healthy, aged 30, and were not related. Racial intermixture in their antecedents was not known. A 2-year-old brother was normal. There was no history of congenital or acquired disease of the blood. During pregnancy there had been no evidence of illness, intoxication, or irradiation.

The father's blood-group was ARh+, and that of the mother was:

$O_{\alpha\beta}$, MNP+, CcDEe/C −K −F (a+)

The blood-group of both infants was:

A_{α_2}, MNP+, ccDEe/C −K −F (a+)

The twins were almost certainly monozygotic. No antibodies against leucocytes were demonstrated in the serum of the mother or the infants.

Necropsy Findings

Necropsy was performed immediately after death, and the pathological findings were identical in both infants. Thymus tissue was nearly absent. No gross abnormalities were found in the internal organs. No lymph-nodes, tonsils, or Peyer's patches were detectable (not verified histologically). Microscopic examination showed remarkable pecularities in the reticular tissue of the spleen, thymus residues, and bone-marrow.

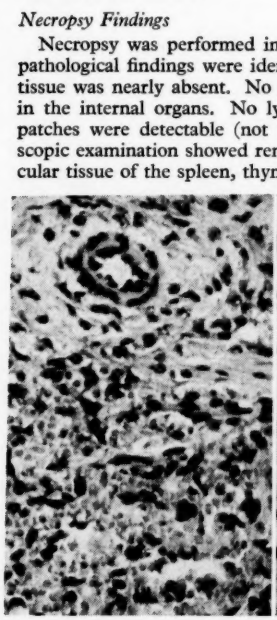

Fig. 1—Spleen of case 1. (Hæmatoxylin and eosin. × 320.)

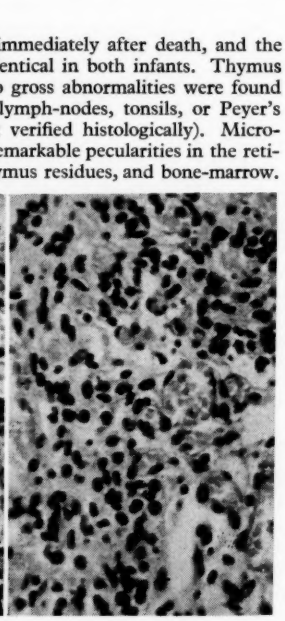

Fig. 2—Thymus of case 1.

Spleen (fig. 1).—The development of follicular structures around the central arteries seemed to be totally lacking. There were no malpighian bodies, lymphocytes, or plasma-cells. The sinuses were dilated and filled with blood. Erythrophagocytosis by large macrophages appeared to be going on in the sinuses but not in the pulp. There was no evidence of extramedullary hæmopoiesis. The capsule appeared normal. The size and weight (about 10 g.) were within the normal range.

Thymus (fig. 2).—Amongst small islets of embryonic fatty tissue was a reticular structure with a distinct reticulin framework. This tissue, which also contained large phagocytic reticular cells, was completely devoid of lymphocytes. There were no Hassall's corpuscles.

Bone-marrow.—Ordinary smears of aspirated marrow, made on the 2nd day of life, were technically imperfect. Smears taken at necropsy (fig. 3) showed fairly normal erythroid development: reticular cells were abundant, and megakaryocytes seemed to be present in sufficient numbers. No distinct myeloblasts, promyelocytes, myelocytes, metamyelocytes, band or lobulated forms, lymphocytes, or plasma-cells could be found. In the bone-marrow sections (fig. 4) the same picture was encountered: distinct reticular tissue with erythroid cells and megakaryocytes, but no myeloid or other elements.

Fig. 3—Case 1. Bone-marrow smear taken at necropsy. (May-Grünwald Giemsa. × 800.)

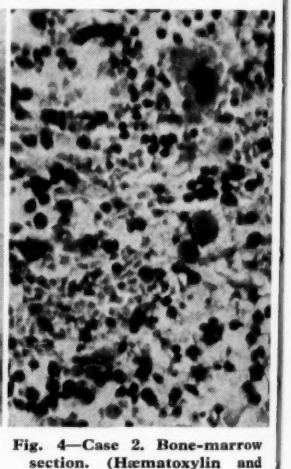

Fig. 4—Case 2. Bone-marrow section. (Hæmatoxylin and eosin. × 320.)

In the blood-vessels, even when dilated and filled with blood, white cells were constantly absent. No histological abnormalities were seen in the other organs. No extramedullary hæmopoiesis was detected in the liver or any other tissue.

Virological investigations of body-fluids and tissues obtained at necropsy were negative with all available techniques.

Discussion

Our case seems to bear no relation to known agranulocytic diseases (Kostmann 1956, Stefanini et al. 1958, Hedenberg 1959; see also Wolman 1957). The recently described forms of alymphocytosis (Glanzmann and Riniker 1950, Donohue 1953) are more nearly related. The link between these syndromes and the antibody-deficiency syndromes (low-resistance syndromes) described by Barandun et al. (1958) has been demonstrated by Cottier (1958), Hitzig et al. (1958), and Guichard et al. (1959).

Antibody formation originates in plasma-cells and lymphoid-tissue cells (Marshall and Cavanagh 1956, Bridges et al. 1959, Henley 1959). In our cases a remarkable and severe abnormality of the reticular tissues existed. This can be regarded as a dysgenesia, the multipotent primitive reticular cells having failed to develop into the mother cells of the myeloid series, or

into lymphocytes or monocytes. These cells were almost absent in the reticular tissue and peripheral blood, but the formation of erythroblasts and megakaryocytes was not disturbed.

We suggest the name reticular dysgenesia for this developmental disturbance, of which we have been unable to find another example, except in an incomplete form. The defect can apparently reach several grades of severity. If the myeloid series is not completely suppressed, the pictures of lymphocytophthisis (Glanzmann and Riniker 1950) and alymphocytosis (Donohue 1953) will result. It seems to offer an anatomical basis for the recent concepts of antibody-deficiency syndromes. The immunological state of the body—which is based on humoral factors (certain γ-globulins and β-globulins) and on the function of the cellular elements—probably determines the clinical picture.

When the reticular system is affected primarily but only partially, the disease seems to show exacerbations and remissions which perhaps depend upon infections and stresses encountered during postnatal life. Thus many diverse clinical pictures and syndromes, apparently incompletely related, can be classified on a functional and anatomical basis. Congenital aleukia seems to be the most severe hæmatological expression.

Because plasma-cells are normally absent from the bone-marrow and spleen of the newborn, whether premature or full term, this finding in our cases does not strengthen the above view. No immunochemical support could be expected, for it is well known that maternal serum-proteins pass to the fœtus. Therefore no further interpretation of our data seems justified. In suspected and proven cases of antibody-deficiency syndromes immunoelectrophoretic analysis and cytohistological examination of the reticular tissues will be needed to test the validity of our concept.

We acknowledge gratefully the help of Dr. H. M. v. d. Linde, pathologist, Onze Lieve Vrouwe Gasthuis; Dr. R. van Dam, pathologist, Binnengasthuis; Dr. F. Dekking, bacteriovirologist; Dr. S. I. de Vries, hæmatologist, Wilhelminagasthuis; and Dr. J. J. van Loghem, head of the Central Blood-transfusion Laboratory, all of Amsterdam.

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Preliminary Communication

BONE MATRIX AND OSTEOPOROSIS

EARLIER this year Buhr and Cooke [1] produced clinical evidence consistent with the hypothesis that senile osteoporosis is a generalised disease rather than a normal ageing phenomenon.

In investigating this hypothesis we began by examining the calcified portions of bones. X-ray diffraction examination of the mineral salts in femurs from a wide age range (the older age-groups containing both normal and osteoporotic bones) showed no distinction between osteoporosis and normal ageing.[2]

Next we studied the collagenous matrix. The basis of the method used is, briefly, as follows:

Electron microscope observations and solubility experiments using diluted acid buffers, as reported on many occasions, have indicated differences in both appearance and behaviour between collagens from different connective tissues. By treating native collagens with alkali, Courts [3 4] has attempted to convert them into fundamental collagen units (eucollagen). Substantial proportions of collagens thus treated will dissolve in citrate buffers.

This treatment was applied to the organic matrix of compact bone, and the different fractions obtained were examined by means of X-ray diffraction, using a fibre camera. Cortical bone from the human femur was used, the age range being from birth to 87 years.

Adhering soft tissue and cancellous bone were removed mechanically and the femur shaft sawn into 1 cm. wide semicircles. The pieces were defatted with trichlorethylene, air-dried, and demineralised in 2*N* HCl at 20°C for 1 week. The conversion to eucollagen was affected in 6–10 days by

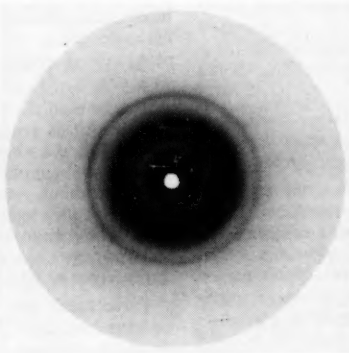

Fig. 1.

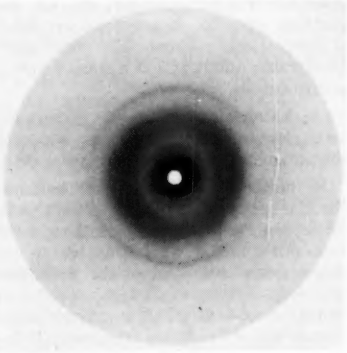

Fig. 2.

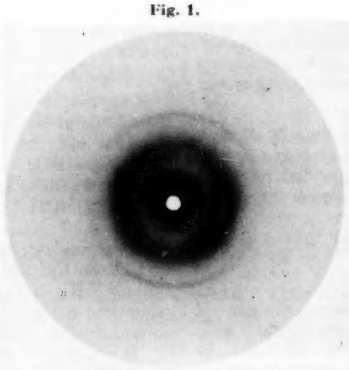

Fig. 3.

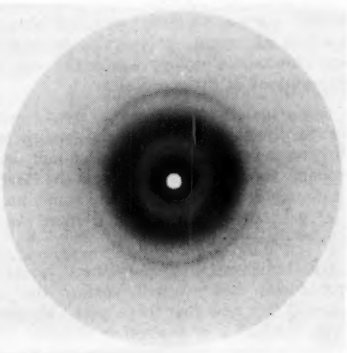

Fig. 4.

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2. Holdoway, E. M., Buhr, A. J., Little, K. To be published.
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1·5*N* NaOH in the presence of 20% Na_2SO_4, which acted as a swelling restrainer. Treatment with 0·1*M* citric acid, pH 2·2, removed the first collagenous fraction to be investigated.

There was a greater proportion of the acid-soluble collagen in infants than in the elderly; but, when separated and precipitated, these samples all gave the same diffraction pattern (fig. 1). The insoluble fraction gave a second diffraction pattern (fig. 2). The characteristic 2·86Å spacing is the same for both, but differences in position and intensity of reflections in the 4–5Å range are consistent with a real chemical difference, analogous to those between different members of the nylon family,[5] rather than a physical difference. In the case of samples from aged people, diffraction rings of the saturated fatty acids were superimposed on the collagen diffraction pattern (fig. 3). This suggests that an increased ease of hydrolysis of esters of fatty acids associated with collagen might be a characteristic of normal ageing of bone matrix.

5. Little, K. *Brit. J. appl. Phys.* 1959, **10**, 225.

When samples of bone from patients suffering from osteoporosis were subjected to the same treatment, the collagen dissolved by the citric acid and then reprecipitated gave the diffraction pattern of fig. 2—that normally produced by the insoluble residue. The residues gave a third and very characteristic variant (fig. 4). That the diffraction patterns show such a clear distinction between the collagenous matrix in normal ageing and that in osteoporosis suggests that in osteoporosis there is a change in the structure of the collagen.

The results of these and related experiments will be published in detail elsewhere. We are grateful to Mr. A. Porter for his help in the preparation of the illustrations.

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Medical Societies

ROYAL SOCIETY OF MEDICINE

THE Use and Abuse of Antibacterial Drugs was discussed on Dec. 4 by the Section of Otology, under the presidency of Mr. R. G. MACBETH, who said that the advent of the antibiotic drugs had been one of the two major influences on the course of otology in the past decade or two. (The other was the dissecting microscope.)

Dr. MARY BARBER said that the bacteriology of *acute* otitis media was relatively simple; for the vast majority of these infections were due to gram-positive cocci. 70% were caused by *Streptococcus pyogenes*; the pneumococcus accounted for a considerable number; and a small proportion were due to the staphylococcus.

The bacteriology of *chronic* suppurative otitis media was much more varied; and proteus, *Pseudomonas pyocyanea*, and other gram-negative organisms were commonly found.

Dr. Barber divided the available antibiotics into three groups. The first group included penicillin, erythromycin, novobiocin, vancomycin, and ristocetin; the gram-positive organisms of acute otitis media were sensitive to all these drugs. The second group consisted of the broad-spectrum antibiotics—streptomycin, chloramphenicol, and the tetracyclines. Streptomycin, she said, should be used only in tuberculous infections, and none of these broad-spectrum antibiotics should be used in simple acute otitis media; but it was sometimes justifiable to use them in chronic suppurative otitis media when no suitable alternative drug was available. The final group included neomycin, polymyxin, bacitracin, and gramicidin; their only use in otology was in the local treatment of chronic suppurations of the middle-ear cleft.

As for toxicity, streptomycin itself most commonly affected the vestibular division of the eighth cranial nerve, while dihydrostreptomycin caused so much deafness that it would probably soon be withdrawn from the *Pharmacopœia* altogether. Deafness was also common, and sometimes very severe indeed, after vancomycin, especially if there was any difficulty with urinary excretion.

Dr. Barber emphasised the need for strict asepsis in surgical procedures, and warned against the possible dangers of ignoring this now that there were so many antibacterial drugs. Drug resistance was another danger, but the streptococcus had so far kept a "fairly clean bill". Nevertheless, if penicillin was used for a streptococcal infection, the patient with staphylococci in the nose might develop a resistant strain and could then be a menace to others. There was convincing evidence of growing resistance of staphylococci to penicillin; but some figures from Washington suggested that, with a controlled antibiotic policy, this trend could be checked. It could also be checked by careful control of the prophylactic use of penicillin.

Severe and even fatal anaphylactoid reactions could follow the use of penicillin—these occurred possibly in 1 per 100,000 cases treated with this antibiotic—but if reports of such reactions gave the impression that penicillin was not very safe, it should be remembered that penicillin was used far more often than its rivals. Other severe reactions included superinfections (usually in the form of enterocolitis), skin reactions, blood dyscrasias, and angioneurotic œdema. All of these could endanger life.

Dr. P. A. WALFORD (Dunmow, Essex), defining what he meant by otitis media, declared that, except when otherwise stated, he used the term not for a discharging ear but for one with an intact drum, bulging or otherwise. The discharging ear, he felt, did not present much of a problem; but when the drum was bulging, was it permissible to "bung in" antibiotics without paracentesis? Would this leave sterile pus? And if it did, would this be followed by organisation, and possibly by deafness? Should we delay the use of antibiotics until rupture had occurred? Or was it better not to let it rupture but to do a paracentesis?

Paracentesis was a very inconvenient procedure in general practice, and for this reason it had practically died out. Figures from the Medical Research Council (1957) had shown that only 1 such operation had been done in 1300 cases of otitis media treated in twenty-eight practices. And of this large number only 1% had been referred to the consultant—usually (he thought) after complications had developed.

If antibiotics were not given, would the incidence of acute mastoiditis grow again? Certainly the incidence of this complication had diminished since the antibacterial drugs had become available; but he had no doubt that this was due, at least partly, to a decrease in the virulence of the organisms. Was one justified, then, in using the antibiotics without a paracentesis? Young and Simson Hall had treated 46 cases with bulging drums in this way and reported no ill effects; and Dixon had reported a similar series in which he noticed no harm. But it was one thing to treat these cases in hospital, where the patient could be watched, the drug could be given intramuscularly, and one could be certain that he was getting it. It was quite a different thing to treat them at home, giving the mother a bottle of oral penicillin; she would give it only when she remembered it or when her child would take it; as

soon as the earache had gone, many a mother would give up the struggle, and Dr. Walford thought that this oral treatment was unlikely to be carried on for more than two days. (Wheatley had shown that 88% of general practitioners who prescribed penicillin gave it orally.)

The 1957 M.R.C. survey had shown that most cases of otitis media were treated in general practice by penicillin, mostly by mouth. In some quarters the results had been hailed as a "triumph for penicillin"; but a few general practitioners who used it only in a few selected cases, treating the others without antibiotics, claimed as good results as those who used it in all cases. 35 of the patients in the M.R.C. study had been left with perforations, dry or moist—an incidence of no less than 3%. Dr. Walford thought that this was a very poor figure. One should always aim at preventing the "disaster of the unhealed perforation"; and it should *always* be possible to get an acute perforation to heal up, provided that the disease was treated properly at the right time. He personally had had no unhealed perforations in thirteen years, and Fry had obtained the same satisfactory result in 1100 cases.

The M.R.C. figures showed that deafness followed otitis media in no less than 10% of cases; and, although their figures were open to objections, he was convinced that this incidence was much higher than in his own series, in which only selected cases were treated with antibiotics. A tendency to relapse after penicillin treatment might account for some of the cases of residual deafness; residual deafness seemed more likely to follow the use of oral penicillin than of intramuscular penicillin.

Dr. Walford did not advocate the total abandonment of penicillin in otitis media. In a small proportion (4%) he used antibiotics because of the severity of the infection, but his chief indication was otitis media complicating some other infection, such as pneumonia or follicular tonsillitis. Whatever the drum looked like, he always used 1% ephedrine and glycerin eardrops to relieve the pain. If pain persisted after twenty-four hours he gave penicillin for at least five days. He preferred intramuscular penicillin, but admitted that he sometimes gave way. If the drum had perforated, he used the same drops and also gave penicillin. It was most important to stop the discharge within two weeks. If it went on for longer than this, many patients would be left with some deafness.

Mr. J. H. OTTY (Bradford) said that in 1946 he had treated two small series of cases of otitis media—15 with sulphonamides, 32 with penicillin. The incidence of mastoidectomy was much lower in the patients treated with penicillin, and its advantages were soon evident. Between March and May, 1947, he treated 37 cases of otitis media, with or without surgical mastoiditis, with penicillin and myringotomy. In no case was mastoidectomy necessary; all the tympanic membranes healed and all the ears became dry.

The dosage of penicillin in these 37 cases was only 20,000 units every three hours. He had changed to a dosage of 1 million units immediately, followed by 500,000 units night and morning, intramuscularly, but did not do myringotomy. Still his results were very good; still the ears were healed and dry in five to seven days; nor did he find any difference in the incidence of residual deafness. It was now the exception rather than the rule for him to do a myringotomy. Of 133 unselected cases treated in this way, with Cavanagh and Jones, between 1954 and 1958, only 13 failed to resolve completely; and of these 13 failures, 10 were found to have chronic, not acute, infections.

Mr. Otty had used oral penicillin in his wards only for three weeks, after which his ward sister had implored him to "go back to the injections: these children are not getting better." He had gained the impression that oral penicillin was responsible for many of the failures and for the rare cases of acute mastoiditis.

He did not use antibiotics extensively in chronic suppurative otitis media, for he was convinced that this type of infection was often associated with irreversible bony changes and the problem was largely surgical. Careful toilet was useful, but boric and spirit drops were just as effective as the antibiotics and they were much cheaper. Nor did he use the antibiotics much in otitis externa, but furunculosis responded well to intramuscular penicillin.

Mr. Otty was impressed by the number of cases of otitis media in which the clinical response to intramuscular penicillin was perfectly satisfactory despite apparent resistance in vitro; it was the treatment of choice in these cases. The antibiotics had a doubtful place in the treatment of chronic middle-ear infections, and he thought that it was unwise to give small doses of the sulphonamides or antibiotics over weeks or even years to children who tended to have recurrent attacks of upper-respiratory infections. The antibacterial drugs should, in fact, be kept in reserve for serious infections.

Dr. T. A. A. HUNTER (Marlborough), as medical officer to a large public-school, saw 30 cases of acute otitis media a year. In twelve years only 1 boy had a discharging ear, and this (he thought) was inherited. His present practice when the drum was only injected was to give $1^1/_2$ million units of procaine penicillin by intramuscular injection and to follow this with penicillin V by mouth. He had yet to see a case which did not subside in two to three days. He was convinced that half the reason for the bad name of penicillin was that too often it was not given in effective dosages at the onset of the infection.

Mr. I. SIMSON HALL (Edinburgh) stressed the importance of myringotomy. One of the most urgent indications for this operation was pain. "It is unthinkable to withhold myringotomy under these circumstances." Another outstanding indication was the bulging drumhead with obvious depression of hearing. It was wrong to let the drum perforate spontaneously, for the subsequent scarring would lead to formation of fibrous tissue, with impairment of function. Deafness was also more likely to persist if the discharge was allowed to continue. Mr. Simson Hall thought that the prophylactic use of penicillin was still permissible in permeatal tympanotomy.

Mr. G. H. BATEMAN also urged the need to do a myringotomy when it was indicated. Before the days of antibiotics, it was necessary to treat the ear and let the body look after the organism: now there was a tendency to treat the organism and ignore the ear. Both approaches were still necessary; penicillin was the treatment of choice for the organism, but one must still look after the ear. Myringotomy was an important step when there was pus in the ear, and, although he thought it was all right for Dr. Hunter to treat his very early cases without incision, the cases he saw in hospital often had a red, bulging, thick drum. These should be treated by myringotomy *and* penicillin.

Mr. P. G. SCOTT (Exeter) agreed that myringotomy could be withheld in very early cases but felt that, when indicated, it could prevent the now uncommon complication of mastoiditis, and it was much less likely to be followed by impairment of function. One of the dangers of the antibiotics, he thought, was that both doctor and parents could be misled by them, with the result that deafness tended to persist longer and might be permanent.

Mr. S. R. MAWSON endorsed Mr. Bateman's views about the need for myringotomy. It should always be used to relieve tension, and an incision with a sharp knife was likelier to heal than was a natural, spontaneous rupture of the drumhead.

Mr. WILLIAM MCKENZIE had heard several of his colleagues in general practice expressing some doubt about the wisdom of admitting these children to hospital for treatment. Their separation from home might cause psychological upsets.

In conclusion, the PRESIDENT said that it was too often forgotten that many mild cases of otitis media would get better with "aspirin and a hot-water bottle".

Reviews of Books

Speech and Brain Mechanisms

WILDER PENFIELD, director, Montreal Neurological Institute, LAMAR ROBERTS, chief of neurosurgery, University of Florida Medical School. Princeton, New Jersey: Princeton University Press. London: Oxford University Press. 1959. Pp. 286. 35*s*.

IN this book Dr. Penfield gives his views—derived from unrivalled experience in brain surgery—on speech, consciousness, and memory and their neurological background. He regards three cortical areas as important for speech. In addition to the accepted frontal (Broca's) and temporoparietal (Wernicke's) areas, he finds evidence that injury to the supplementary motor area on the medial aspect of the dominant hemisphere may cause transient dysphasia and that stimulation will also cause arrest of speech. On consciousness and memory he is impressed by the fact that electrical stimulation of certain areas of the temporal cortex will reproduce past experience with all its earlier perceptual surroundings, suggesting that some storage mechanism for the stream of consciousness is being artificially brought into action. He points out also that electrically recalled events for the patient differ from his ordinary memories; voluntary recall not having the same experiential completeness. His evidence assigns to the temporal cortex functions of recall, comparison, and interpretation of past experience—memory in a full sense. Though not all will agree with his interpretations, his observations which he gives in full are of the utmost interest and importance. Although Dr. Penfield is the senior author, Dr. Roberts has contributed considerably to the work—especially on the question of handedness and hemisphere dominance.

Rheumatic Fever, Epidemiology and Prevention

A Seminar at the International Children's Centre, Paris, September, 1956. Editors: ROBERT CRUICKSHANK, M.D., F.R.C.P.; A. A. GLYNN, M.B., M.R.C.P. Oxford: Blackwell Scientific Publications. 1959. Pp. 193. 25*s*.

THIS kind of book, assembled as quickly as possible from contributions at a conference, is inevitably patchy. Most of this one is devoted to the theme that group-A β-hæmolytic streptococcal throat infection may lead to rheumatic fever, and therefore the more we know about the streptococcus and how to prevent or cure streptococcal infections the less rheumatic fever and heart-disease shall we have. Between Wahl's excellent review of the bacteriology and immunology of the streptococcus and Rutstein's equally able account of the practical applications of present knowledge are to be found some first-class papers. The reviews by Mozziconacci and Labesse, for example, on the prevention of first attacks and recurrences of streptococcal infection are models of clarity. Here and there is a different note which suggests that non-streptococcal factors are also important: Jersild's survey of rheumatic fever in Denmark (where the disease has been notifiable since 1878) exemplifies the remarkable and steady decline of this disease long before pasteurisation of milk (1920) or sulphonamides (about 1938) were introduced in Denmark. Bywaters considers the evidence for the inheritance of rheumatic fever and describes the possibility that secretor-status may predetermine susceptibility. But most of the book is about streptococci and how to control them; and there the outstanding weakness seems to lie in the detection and control of nasal carriers. Publication was delayed by the death of Dr. Raymond Gautier, who prepared the original French edition.

Dr. Jenner of Berkeley

DOROTHY FISK. London: Heinemann. 1959. Pp. 288. 25*s*.

SOME twenty miles from Bristol there stands, in the grounds of a modest but elegant country house, a small hut. It is a mere one-roomed structure of brick, thatch, and untrimmed boards. Not a doctor in a thousand would recognise a photograph of it, and even fewer can claim to have visited it. None the less it is a medical shrine as deserving of veneration as the operating-theatre of Massachusetts General Hospital, or Harvey's last resting-place in Hempstead Church. For in this " Temple of Vaccinia ", as he called it, Edward Jenner inoculated his neighbours, and demonstrated how a disease which was killing over forty thousand inhabitants of these islands every year might be abolished completely.

Jenner has always been a favourite subject for biographers. He cuts a rich figure in his successive roles of naturalist, poet, country practitioner, and internationally famous physician. His life is abundantly documented, and he would be a dull writer who could make nothing out of a character who would have been remembered as Hunter's first pupil, and for his investigation of the breeding habits of the cuckoo, even if he had never given a thought to cowpox. But no-one has yet breathed as much life into the facts of Jenner's career as Mrs. Fisk has done, and none of them has eluded her. He is recognised as having been the first to describe coronary atheroma—a distinction which even Garrison overlooks. (And Garrison also errs in affirming that Jenner died in London: he passed away in his beloved Berkeley, Gloucestershire, and the chapters describing his last years are among the best in this book.)

Mrs. Fisk's erudition and easy style combine to make this a model of all that a medical biography for popular consumption should be.

The Very Error of the Moon

THEODORE G. GRAY, C.M.G., M.B., F.R.A.C.P., formerly director-general of mental hospitals in New Zealand. Ilfracombe: H. Stockwell. 1959. Pp. 191. 15*s*.

Dr. Gray has given us a number of random and whimsical reminiscences from a long medical life which started as a student in Aberdeen at the turn of the century. His short account of life at Kingseat Mental Hospital near Aberdeen and of developments he brought about overseas reminds us that reform in psychiatric administration is not always as new as it seems, and Dr. Gray might profitably have expanded this part of the book at the expense of rather random recollections of travel in America and France which gave him so much pleasure and interest. He writes entertainingly with abundant anecdotage, and the book will give a few hours' gentle enjoyment.

Synopsis of Ear, Nose, and Throat Diseases

ROBERT E. RYAN, M.D., M.S., F.A.C.S., department of otolaryngology, St. Louis University School of Medicine; WILLIAM C. THORNELL, M.D., M.S., F.A.C.S., assistant professor, department of otolaryngology, Cincinnati College of Medicine; HANS VON LEDEN, M.D., F.A.C.S., assistant professor of otolaryngology, Northwestern University Medical School, Chicago. St. Louis: C. V. Mosby. 1959. Pp. 383. 50*s*.

HERE the common diseases of the ear, nose, and throat are presented concisely, and their ætiology, pathology, symptoms, prognosis, and treatment are outlined. A crisp summary of the main symptoms and treatment at the end of each chapter is useful for quick reference. Except for the chapter on laryngeal paralysis, the views reflect generally accepted principles of practice in the United States. The style is brisk and easily readable. The index is good and the book is attractively presented under clear-cut headings.

Treatment of Cancer and Allied Diseases (2nd ed. Vol. 2. *Tumours of the Nervous System*. London: Pitman Publishing Co. 1959. Pp. 316. 105*s*.).—The second of nine volumes, edited by Dr. George T. Pack and Dr. Irving M. Ariel, on the treatment of cancer and allied diseases deals with tumours involving the central and peripheral nervous systems and also the sympathetic system. There are chapters on the relief of pain in malignant disease by nerve-block and by operations such as spinothalamic chordotomy and prefrontal leucotomy. Some account is given of the pathology of the tumours and of special methods of investigation, but most of the chapters contain a detailed and somewhat didactic account of surgical methods of treatment, with a less detailed account of radiotherapeutic methods. The book is profusely illustrated and usually well.

THE LANCET

LONDON 19 DECEMBER 1959

Oral Hypoglycæmic Agents

THE era of treatment of diabetes by oral hypoglycæmic agents is now well started, and it is appropriate to reflect at this point whether early enthusiasm has made too light of some of the disadvantages of these drugs, the long-term effects of which are, of course, still unknown. The standard of reference for all such compounds is the established information on the effects of insulin. If the sulphonylureas or the diguanides can produce as good overall control of diabetes as insulin without more unpleasant side-effects, their oral administration will offer a clear advantage. But at this stage in their development the oral hypoglycæmic can be considered as an alternative to insulin in only certain types of diabetes. Thus apparently some endogenous insulin must be present for the sulphonylureas to be effective [1]: which eliminates as potential recipients of this treatment nearly all juvenile diabetics and most maturity-onset diabetics who have had ketotic episodes.[2] The diguanides have a wider scope of effective hypoglycæmic action, but even with these a little insulin seems to be necessary to prevent the development of ketosis.[3] If consideration is limited to those diabetics who could have their blood-sugar well controlled by either insulin or an orally administered drug, but not by dietary restriction alone, the main criterion will be the relative toxicity.

The toxic effects of insulin, discounting hypoglycæmia due to an overdose, are fat atrophy at the sites of injection (this is common, especially in women[4]), and very occasional allergy indicated by a rash or, more rarely, by anaphylactoid collapse with dyspnœa,[5] gastrointestinal symptoms,[6] purpura,[7] or resistance to the hypoglycæmic action of insulin.[8] With the sulphonylureas the incidence of toxic effects is beyond doubt significantly higher than with insulin. Thus carbutamide, the first of this series to be released in this country, produced all the complications to which sulphonamides are heir and was eventually discarded in October, 1956, in the U.S.A. after several reports of bone-marrow depression and of jaundice. Tolbutamide, which is not a sulphonamide, was the next in this group of drugs to be released widely and has proved comparatively safe, although by no means altogether harmless. Its toxic effects include relatively trivial rashes and a tendency to flush unduly after taking alcohol,[9] and also—which is more serious—exacerbation of the manifestations of peptic ulceration, including bleeding [10] and perforation,[11] sometimes after many months of treatment, and perhaps, very occasionally, aplastic anæmia.[12] Chlorpropamide is to some extent supplanting the longer-established tolbutamide, since it has a stronger hypoglycæmic action and acts longer [13 14]; but it, too, carries its risks—occasional transient drug rashes,[15 16] rarely obstructive jaundice,[17] fever, and gastrointestinal disturbances [18]—although these seem to be less common than with tolbutamide. Some of the toxic effects, such as vertigo and severe hypoglycæmia, that were reported in the early stages were attributable to excessive dosage in the hands of clinicians used to the dose requirements of tolbutamide. At dose levels of under 500 mg. daily, few unpleasant side-effects arise.

Most investigations of the diguanides have concerned phenethyldiguanide (DB1). With this drug the therapeutic dose is very near the toxic one, which may produce anorexia, nausea, and vomiting and diarrhœa at first, and weakness, lethargy, and weight loss later [19]; but hepatic or renal damage has not been reported, and DB1 is undoubtedly much safer than the chemically related synthalins used in the late 1920s.[20] The hypoglycæmic action of DB1 is less physiological than that of the sulphonylureas, which appear to stimulate the release of endogenous insulin, although the increase in anaerobic glycolysis produced by DB1 can be likened to that in muscle during exercise. In both situations there is a rise in blood-lactic-acid with the production of less energy than is provided by normal aerobic glycolysis. WALKER [21] has shown that the effects of DB1 and exercise are additive; and herein lies potential danger, for the alkali reserve may fall steeply. Moreover in patients receiving DB1 ketosis tends to develop at relatively low levels of blood-sugar, possibly partly owing to DB1's known action of reducing the stores of liver glycogen.[22] One patient affected in this way died in acidosis before effective remedial measures could be undertaken [21]: these measures should clearly consist in the provision of dextrose and insulin and the withdrawal of DB1. It follows that DB1 should not be used with diets of too low a carbohydrate content (perhaps not less than 170 g. daily). According to most reports DB1 produces side-effects which are a nuisance rather than cause for alarm; but at present this drug must still be used with circumspection, perhaps mainly for diabetes which is so unstable as to be very hard to

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manage on insulin treatment alone.[23] In such cases, when the disease is controlled by DB1 and a much-decreased dose of insulin, the tendency to become hypoglycæmic may be reduced. Unlike the sulphonylureas, DB1 does not seem to cause hypoglycæmia in non-diabetic people, although it may do so in animals.[24] Unlike the sulphonylureas too, it does not seem to lose its hypoglycæmic efficacy with long-continued administration: this loss happens in at least 10% of patients given tolbutamide.[25 26]

The proper place of the hypoglycæmic sulphonylureas remains uncertain. Meanwhile their use can be most clearly justified in the case of the elderly diabetic who has not had ketosis but needs more than dietary treatment, who may find self-administration of insulin difficult or impossible, perhaps because of failing vision, and whose disease can be controlled by a suitable diet and chlorpropamide or tolbutamide. Longer experience of the more general use of the sulphonylureas will enable more valid comparisons with insulin treatment to be made. The sulphonylureas may possibly prove of value in the prophylactic treatment of the very mild diabetic or prediabetic,[27] diagnosed by the family history or pregnancy history or by the response to a provocative test with cortisone [28] or prednisone.

Trophoblast and its Tumours

THE papers submitted to a conference on trophoblast, held by the New York Academy of Sciences in October, 1958, have now been published in the academy's *Annals*.[29] Here is to be found the most complete account of the trophoblast and its neoplastic potentialities which has yet appeared.

A new interest in gestational trophoblast, and a new stimulus to research directed towards elucidating the cause and cure of its tumours, have been provided by the realisation that trophoblast is a homograft (i.e., a tissue implanted into a donor of the same species), half of its genic material being maternal and half paternal. Apart from the successful exchange of homografts between monozygotic twins, the life of a homograft such as a piece of skin is no more than ten to fifteen days, compared with which the survival of human trophoblast for forty weeks is lengthy. The reason for this long survival is uncertain, though it is known that the homograft reaction (i.e., the failure of the grafted tissue to continue to grow in a host of the same species) can be abolished by exposing an animal in fœtal life to cells from its donor; this enables the animal, which has "acquired tolerance" [30], later in life to accept grafts from the donor. MEDAWAR and his colleagues [30] say: "Every degree of tolerance is possible, from that which allows a homograft to live only a few days beyond its normal median expectation of survival to that in which it is permanently accepted by and incorporated into its host." Thus the forty-week survival of trophoblast may be regarded as an expression of prolonged homograft tolerance; and the degenerative placental changes before term constitute evidence that this tolerance is beginning to wane. Does tolerance lie in the fact that trophoblast is an offspring-to-parent graft which is antigenically immature? An answer may be sought by comparing the behaviour of embryo-to-mother and embryo-to-stranger grafts,[31] or by experiments which might throw light on why the fœtus itself does not suffer the fate of a homograft. WOODRUFF [32] suggests that the fœtus is protected because it is anatomically separated from the mother and thus antibody-carrying maternal cells cannot reach it.

The main achievement of the New York conference was to emphasise the fine gradations of growth and dissemination of trophoblast which may take place in the maternal organism in various circumstances. As far as local growth is concerned, there is gradation from normal cytotrophoblast through moles of various degrees of proliferative growth to choriocarcinoma. The names of these conditions have too many meanings for the comfort of the hospital pathologist and clinician. There is much to be said for retaining "cytotrophoblast" for the normal chorion, with hydatidiform mole, destructive hydatidiform mole (or chorioadenoma destruens), and choriocarcinoma for the gradation of proliferative lesions.

PARK [33] analysed the opinions given by four or five pathologists on the nature of the lesion in each of 200 cases of trophoblastic abnormality. There was no difficulty in the diagnosis of simple abortion or hydatidiform mole, except that in the latter case some pathologists raised the question of "suspicious" when others did not. But of the 89 cases where the question of choriocarcinoma arose, in only 30% did all the examiners agree on the diagnosis; and in half the cases the histological pattern was interpreted in opposite ways by one or more of the examiners, sometimes even when the excised uterus was available for examination. These findings show clearly how great is the difficulty in diagnosing malignant trophoblastic lesions and that this difficulty is not confined to uterine curettings.

PARK raises the question whether in trophoblast a histological pattern diagnostic of cancer actually exists. In other words, can tissue of the same appearance as that obtained from a patient who has died of metastasising choriocarcinoma be present in the uterus without necessarily presaging metastases and death?

SCHMORL [34] described multinuclear cellular fragments in the smaller pulmonary vessels of eclamptic women who had died during seizures or shortly after delivery. Syncytial embolism in normal pregnancy is now recognised as common. Both BARDAWIL and TOY [35] and PARK [36] have extensively investigated the lungs after death during pregnancy. In roughly half of 300 cases

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34. Schmorl, C. G. Pathologisch-anatomische Untersuchungen über Puerperal-Eklampsie. Leipzig, 1893.
35. Bardawil, W. A., Toy, B. L. *Ann. N.Y. Acad. Sci.* 1959, **80**, 197.
36. Park, W. W. *ibid.* p. 257.

trophoblastic embolism was observed, but in only 2 were apparently normal chorionic villi seen. Four factors might be expected to influence the amount of trophoblast passing to the lungs: (1) the nature of the illness causing death (for example, circulating trophoblast is associated with eclampsia); (2) the gestational age of the trophoblast, because young trophoblast is more invasive than old; (3) the degree of uterine contraction (e.g., after prolonged obstructed labour); and (4) the time elapsing between separation of the placenta and death, as trophoblast might survive for no more than a few days in the lung. After analysing 53 cases PARK concluded that the most important factor causing trophoblast to pass to the lungs was the process of separation of the placenta, or "placental commotion", excessive uterine contraction having a similar, though less pronounced, embolism-promoting effect. PARK raised a doubt as to whether particles of trophoblast pass continuously to the lungs throughout normal pregnancy, and pointed out that what is seen in the lungs of patients who have died after delivery is almost certainly no true indication of what obtains in pregnancy up to the onset of labour. PARK also concluded that the maximum length of survival of a particle of normal trophoblast in the lungs is of the order of only three days.

In sharp contrast are the recently described cases of choriocarcinomatous embolism in the lungs [37 38] (in two of which choriocarcinoma was found at necropsy in the pelvic veins also [37]). The striking common feature of these cases was the presence of proliferating trophoblast in the pulmonary arteries and completely delimited by the arterial wall. These vessels may be normal, or they may be thickened and inflamed; and in the latter event they exhibit intimal proliferation, fibrinoid necrosis, and adventitial cellular hyperplasia [39]; which might be interpreted as an allergic or sensitisation reaction. FAHRNER et al.[38] thought that the tumour emboli had been present in their patient for a year before death. It is thus clear that, in contrast to metastatic choriocarcinoma of the classical dramatic malignant hæmorrhagic type, there is another group of cases in which the proliferating trophoblast is contained in the vascular tree for long periods. Can such a condition account for the rare cases of spontaneous regression of choriocarcinoma, of which only 20 reported instances were acceptable to PARK and LEES [40]? Can it be, as GREEN [41] suggested, that invasion by malignant trophoblast is common but often the host destroys it. In CHUN and HOU'S case [42] pulmonary metastases regressed but necropsy revealed that death was due to cerebral metastases. Spontaneous regression has not been reported in cases of choriocarcinoma arising from testicular teratomas. This, and the failure of LI et al.[43] to ameliorate the disease in males by means of methotrexate, are additional reasons to those advanced by WILLIS [44] for supposing that there is no such thing as male choriocarcinoma.

Finally the New York conference considered the treatment of choriocarcinoma by folic-acid antagonists such as methotrexate. HERTZ et al.[45] claimed that in 5 out of 27 cases complete remissions had been obtained for periods extending from eight to twenty-nine months; and BAGSHAWE and BROOKS [37] reported that 1 patient in their series was doing well on this treatment. OBER [39] gave the latest information about a patient treated by immunisation by her husband's leucocytes combined with administration of methotrexate [46]: a further remission was obtained by another course of methotrexate.

Study of the immune mechanisms concerned in the restraint of unlimited growth of trophoblast and the pursuit of means of immunising the mother against such growth are likely to yield fruitful results before long.

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38. Fahrner, R. J., McQueeney, A. J., Moseley, J. M., Petersen, R. W. *J. Amer. med. Ass.* 1959, **170**, 1898.
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Annotations

THE BROADMINDED SPECIALIST

As his subject for the first Watson-Jones lecture of the Royal College of Surgeons, delivered on Dec. 9, Lord Cohen of Birkenhead chose Specialism; which he thought appropriate because of Sir Reginald Watson-Jones' own outlook on his specialty. He had become a surgeon by choice, an orthopædist by chance; by conviction he had remained a doctor of wide interests.

In the past twenty-five years specialties have proliferated freely, but Lord Cohen thought it a mistake to attribute this solely to the rapid growth of knowledge. Adroitly misquoting Ben Jonson, he affirmed:

> It is not growing like a tree
> In bulk doth make a specialty.

From earliest times the practice of medicine had shown this tendency. It existed in ancient Egypt, and Diodorus Siculus had described there a national health service in which specialists were employed by the State. The abstract idealism of Greece had for a time discouraged specialism, but there was evidence that specialists practised in Rome. In the Middle Ages a good deal of specialist practice devolved on the itinerant quack. Among these colourful, if unorthodox, practitioners the most effective, if not the most dramatic, were the bonesetters. In many agricultural communities there was a family which passed on its skill from generation to generation. The best known of these was of course the family of Hugh Owen Thomas, the patron of modern orthopædics.

Specialism as we understand it today had its origin in the 17th century, when the growth of population and its concentration in large towns offered doctors opportunity to trace the patterns of disease and to classify the different symptoms; and the correlation of clinical and pathological observations continued in the 18th century. In the 19th century man's body was recognised as a physicochemical mechanism and the instruments of physics, chemistry, and biology began to be used for clinical investigation. The ophthalmoscope and its

offspring and in due course X rays soon allowed the doctor to examine, directly or indirectly, every part of the body. These developments created specialties concentrating on different parts of the body, on different parts of the world, on special techniques, on single diseases, and on ideologies, besides the splinter groups of general medicine.

Specialism could inhibit as well as advance both knowledge and practice. For instance, against superlative craftsmanship in an intricate technique must be set over-concentration in a too narrow field, when a symptom might be investigated or treated and a disease and a patient ignored. This danger could also threaten research, and in a team it was important that members should at least be aware of the potentialities of each other's discipline. There was still room for the lone genius who could discern the underlying unity in a diversity of facts and for the observer who gathered information with his own eye, ear, and sympathy without benefit of scientific instruments.

But specialism had obviously and rightly come to stay and we must come to terms with it. As safeguards Lord Cohen urged that the lesson of holism should be taught to the student early in his course—that he should be instructed in the basic principles of medicine and surgery, and urged to reason and think for himself. The present curriculum was too technological; offering a smattering of all kinds of knowledge it had become a " tortuous and ungodly jumble ". Earlier textbooks offered the student the author's philosophy; today they were too often unrelated monographs by different authors—a patchwork quilt instead of a tapestry. It was inevitable that some patients should be treated by congeries of specialists, but many patients felt the need to have someone in continuous charge. This would usually be the family doctor. But it could also be a specialist, provided he was, like Sir Reginald, a specialist who was also a guardian of the principles of medicine and surgery and imbued with the concept of holism.

SMOKING AND "CHRONIC BRONCHITIS" IN THE U.S.A.

GROWING evidence points to an association between cigarette smoking and obstructive lung disease,[1–11] and now Flick and Paton [12] report from the U.S.A. the results of an investigation designed to throw further light on this relation. They examined 222 male hospital patients most of whom were ambulatory and awaiting elective surgery, convalescing from various diseases, or under investigation or treatment. They excluded from the study those with advanced granulomatous lung disease, recent pyrexia, congestive heart-failure, previous thoracic operations, a history of asthma since childhood or adolescence, a history of having stopped smoking, or illness so severe as to preclude satisfactory cooperation in tests of lung function. Only cigarette smokers were classed as " smokers "; pipe and cigar smokers were classed as non-smokers. The maximal expiratory flow-rate (M.E.F.) was estimated in each patient included in the study.

In non-smokers there was no appreciable decline in the M.E.F. until the age of 70 years, and then it was due so far as could be ascertained to general feebleness and not to respiratory disease. In smokers, on the other hand, the M.E.F. declined progressively from the mid 30s. Between the ages of 60 and 70 years there were 20 non-smokers and 61 smokers: the mean M.E.F.s were 378 and 258 litres per minute respectively—a highly significant difference ($P < 0.001$). The M.E.F. tended to vary inversely with the total amount of tobacco that had been smoked, and smokers who left long cigarette butts tended to have a higher M.E.F. than those who left short ones. The range of M.E.F. values was greater in smokers than in non-smokers—a feature which Flick and Paton thought might be due to the varied effects of smoking in different people. Proportionately more smokers than non-smokers admitted to having a cough, raising sputum, and being liable to " colds settling in the chest ".

Flick and Paton concluded that cigarette smoking is liable to produce obstructive emphysema, and that in most cases it is the most important causal factor. They define obstructive emphysema as a condition characterised by dyspnœa, persistent or recurrent cough, and the production of viscid mucus especially in the morning, and regard it as secondary to bronchiolar inflammation: clearly this condition is the same as that usually termed in this country " chronic bronchitis ". From their findings it might therefore reasonably be inferred that the prevalence of chronic bronchitis in the U.S.A. does not greatly differ from that in this country, and other evidence [13] supports this conclusion. But if this estimate is correct it is surprising that, according to official statistics, the death-rate from chronic bronchitis is 45 times greater in England and Wales than it is in the U.S.A.[14] Possibly deaths which would be attributed to chronic bronchitis in this country are classified under some other heading in the U.S.A., but Fletcher [14] thinks that, while important discrepancies in nomenclature undoubtedly exist, the difference in mortality-rates is nevertheless substantial and is much greater than the difference in prevalence. If this is so, and if cigarette smoking is a major factor in the causation of chronic bronchitis, then the heavier mortality in England and Wales must apparently be attributed to some potentiating factor. Fletcher [14] suggests that this factor should be sought in the environment of the poorer social classes of this country; for in England and Wales it is in this section of the population that mortality is highest.[15]

In order to learn more about the ætiology of chronic bronchitis, we must gain more accurate information about its natural history. A useful step would be the adoption of a standard definition of " chronic bronchitis "; for, owing to the present lack of any general agreement on the meaning of the term, comparison of the findings in different investigations is often difficult or impossible. Even in this country, for some workers " chronic bronchitis " implies disability while for others it does not. Fletcher [14] suggests that the expression " chronic bronchitis " should refer to the " condition of subjects with persistent or recurrent excessive mucous secretion in the bronchi ", and he believes that it would be helpful to classify chronic bronchitis into (*a*) simple chronic bronchitis, in which there is a persistent or recurrent productive cough without dyspnœa or ventilatory impair-

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2. Oswald, N. C., Medvei, V. C. *ibid.* 1955, ii, 843.
3. Palmer, K. N. V. *Brit. med. J.* 1954, i, 1473.
4. Greene, B. A., Berkowitz, S. *Ann. intern. Med.* 1954, **40**, 729.
5. Phillips, A. M., Phillips, R. W., Thompson, J. L. *ibid.* 1956, **45**, 216.
6. Lowell, F. C., Franklin, W., Michelson, A., Schiller, I. *ibid.* p. 268.
7. Clough, P. W. *ibid.* p. 1235.
8. Leese, W. L. B. *Lancet*, 1956, ii, 762.
9. Doll, R., Hill, A. B. *Brit. med. J.* 1956, ii, 1071.
10. Higgins, I. T. T. *ibid.* 1959, i, 325.
11. Fletcher, C. M. Elmes, P. C., Fairbairn, A. S., Wood, C. H. *ibid.* Aug. 29, 1959, p. 257.
12. Flick, A. L., Paton, R. R. *A.M.A. Arch. intern. Med.* 1959, **104**, 518.
13. Pemberton, J. *A.M.A. Arch. industr. Hlth*, 1956, **13**, 529.
14. Fletcher, C. M. *Amer. Rev. Tuberc.* 1959, **80**, 483.
15. Fletcher, C. M. *A.M.A. Arch. industr. Hlth*, 1958, **18**, 368.

ment; (*b*) chronic bronchitis with infection in which there is mucopurulent sputum or recurrent chest illnesses; and (*c*) chronic bronchitis with obstructive lung disease in which there is ventilatory impairment with or without dyspnœa. Subdivision of these categories would indicate the degree of severity. General acceptance of some such classification would be a notable advance.

ANTIBODIES TO COLON IN ULCERATIVE COLITIS

THE widespread efforts to incriminate autoimmune processes in the pathogenesis of obscure diseases are meeting with some encouraging successes. The latest is the demonstration of circulating antibodies in the serum of a high proportion of children with chronic ulcerative colitis.[1]

They were demonstrated by two well-tried techniques —namely, precipitation of the appropriate tissue extract by the patient's serum when these two reagents were allowed to diffuse towards each other in an agar gel, and the agglutination by these same sera of sheep cells suitably coated with similar tissue extracts. To obtain extracts of colon free from bacterial contamination Broberger and Perlmann [1] used colons from infants who had died within 24 hours of birth and had never been fed. The best preparations were obtained with a phenol-water mixture at 65°C, the active material passing into the aqueous phase from which it was subsequently obtained by dialysis and lyophilisation. This material was mainly composed of lipopolysaccharides, and the non-protein nature of the active principle was substantiated by its preferential coating of untanned red blood cells.

The results with sera from 30 children with ulcerative colitis, 38 normal children, and 32 with miscellaneous diseases undoubtedly justify the author's claims. With the precipitin test results were positive in 22 of the 30 test sera, in 3 of the 32 miscellaneous controls, and in none of the normal controls. With the hæmagglutination test the results were even more striking: 28 positives in the 30 test sera, 5 in the miscellaneous group, and none in the 38 normals. With both tests the positives in the miscellaneous group were cases of nephrosis, nephritis, or rheumatoid arthritis. Two further observations strongly support the contention that a true antibody is responsible for the reactions: firstly, saline extracts of lymph-nodes from the subserosal layer of affected colons gave similar reactions; and secondly, by immuno-electrophoresis the activity in both the sera and these lymph-node extracts was found to be associated with the γ-globulins.

In most other diseases, both natural and experimental, in which an autoimmune process has been suspected, the serum antibodies themselves do not seem capable of producing tissue injury. With few exceptions, neither in vivo nor in vitro, has the exhibition of high-titre sera produced demonstrable injury to the tissues rich in the specific antigen. Ulcerative colitis is apparently no exception. When cultures of colon cells were repeatedly exposed to sera from such patients no cytotoxic effect was demonstrated. In view, however, of Pulvertaft's [2] recent results with Hashimoto serum and fresh cultures of thyroid gland these findings must be interpreted with caution. The tissue specificities of cells in tissue-culture are apparently lost as readily as their specific morphological features, or even more readily. Broberger and Perlmann, however, were able to show by the use of fluorescein-conjugated antibody that their colon cells in tissue-culture could still combine specifically with the antibody. The evidence therefore suggests that in ulcerative colitis, as in the majority of diseases suspected of an autoimmune pathogenesis, cell-fixed antibodies may be more important than those in the serum.

If, as this evidence suggests, ulcerative colitis is the result of a specific immune reaction of the body to antigens normally present in the human colon, why do normal individuals fail to respond to their presence? With such a vascular tissue as the intestinal mucous membrane it would seem extremely unlikely that tolerance to the tissue antigens would fail to be achieved through lack of access of these antigens to the antibody-forming tissues in fœtal life. This might not apply, however, to antigens in the secretions themselves. Moreover, the chemical relationship of these secretions to the blood-group substances and the ease with which the antigenicity of these substances is enhanced by adsorption on to microorganisms [3] emphasise their possible role in this capacity.

1. Broberger, O., Perlmann, P. *J. exp. Med.* 1959, **110**, 657.
2. Pulvertaft, R. J. V., Doniach, D., Roitt, I. M., Hudson, R. V. *Lancet*, 1959, ii, 214.
3. Glynn, L. E., Holborow, E. J., Johnson, G. D. *J. Immunol.* 1956, **76**, 357.
4. *Times*, Nov. 10, 1959.

TAMING THE TOUGH?

WHEN the word "teenager" appears in print today, it is often accompanied by the word "delinquent", and we are apt to forget that most young people are leading law-abiding, sensible lives. But though the delinquents are few they are still too many, and their numbers are growing. The bad press that they are getting is a sign not only of justified concern but of an uneasy feeling that somewhere, somehow, the community has failed in the task of bringing them up. Perhaps partly as a result of these mixed feelings the reaction of some people—like the delinquents themselves, probably also a minority—is to meet lawlessness with intimidation. Though there is a place for firm and consistent authority in a child's upbringing, repressive measures can be dangerous in adolescence. The adolescent has a tremendous capacity for rising to challenges—the "revolutionary" phase of normal development is of great social value—but the general denial of authority-figures implicit in adolescent revolt is tricky to handle. In the United States, for instance, where the police are armed and often act ruthlessly, and where reformatories are tough, "teenage problems" are graver than here. This summer in New York alone as a result of gang-fights 11 young people were shot, knifed, or beaten to death, and several adults were killed in attacks by teenage gangsters.[4]

Indignation at violence understandably stirs a desire to punish and exact retribution from a delinquent. But emotion, however natural, is not always the best guide to treatment; and the future of the delinquent is more important than assuaged feelings. There is, and probably always will be, a hard core of dangerous offenders who need management in closed institutions, but these are a small minority of those who pass through our juvenile courts, and it is not in anyone's interests that we should allow the need of this minority to distort our handling of the tractable majority. Violent punishments are useless for the minority and unnecessary for the majority. Any proposal to restore flogging or birching should be strenuously resisted. Many cures attributed to current punitive methods are probably due to the normal maturation process and decline of crime with age.

Apart from these well-tried and largely negative

methods, what have we to offer? Chief of our present positive approaches is the case-work of keen probation officers. In this, coercion and restriction are at a minimum, and the officer can give a stable friendship to the boy or girl. Adequate psychiatric treatment may be useful to a few, but intensive psychotherapy for all delinquents will probably never be practicable, nor indeed desirable. The psychiatrist's chief role will probably be, as it often is at present, to advise teachers and social workers.

Some pioneer ventures have had hopeful results.

Lyward [5] has tackled the problems of the disturbed adolescent of high intelligence. Joyce,[6] in an approved school, has discarded tough punishment, because it makes a lad look on himself as a "tough guy" and act accordingly. In the High Peak national park in Derbyshire, where young people from the cities had been creating havoc, Mrs. Edrie Green [7] formed her own "Teddy-boy gang of mountaineers" and the boys willingly tackled a regime of rough living and hard climbing. To present the elements as a challenge is also the principle behind the Outward Bound system and the North Sea Camp, a borstal where the boys work in land-reclamation. Another positive idea has been tried in Darmstadt,[8] where a judge in the juvenile court orders young offenders to carry out some useful work, preferably relevant to their offences. Thus dangerous drivers may be sent to work every Saturday morning for three months in a hospital casualty ward.

All these techniques depend for success on the personality of the pioneer, and they may not prove successful in other hands, particularly reluctant hands: older methods will not be readily discarded. Whatever the findings of the present approved-school inquiry may be, the evidence has made many people realise for the first time the difficulty and importance of the work that is being attempted.

LIFE WITHOUT WHITE CELLS

THE white cells of the peripheral blood are of two main types—granulocytes and lymphocytes. In some pathological conditions few of one or other of these types of cells are present in the peripheral blood.

Acute agranulocytosis is a grave illness characterised by fever, sore throat, and prostration; the white-cell count in the blood is about 1000 per c.mm. or less, and there may be no granulocytes at all. Examination of the marrow may show only degenerating myelocytes and few of these; or there may be quite a lot of myelocytes, some in mitosis. The first picture indicates that the patient is likely to die, the second that recovery is likely. Acute agranulocytosis is nearly always due to drugs. Wintrobe [9] lists over fifty that have been implicated, and the list is not complete; amidopyrine, thiouracils, and sulphonamides have been most commonly responsible. Chronic neutropenia is rarely fatal; it is often found in children and is sometimes associated with recurrent infection of the upper respiratory tract. The white-cell count in the blood may not be very low, but perhaps less than 10% will be granulocytes. Bone-marrow examination, however, shows an adequate number of granulocytes up to the metamyelocyte stage, and the condition seems to be a defect of final maturation or of delivery of cells from the marrow to the blood. As a rule the condition is not dangerous, and sooner or later the white-cell count in the peripheral blood becomes normal and stays normal. The cyclic neutropenia of adults presents a somewhat similar picture: the patient is not really without granulocyte-forming tissue; the cells are there when needed.

Absence of lymphocytes is much more serious and is fortunately rare, since the patient does not survive long. Glanzmann and Riniker [10] gave an account of two infants, aged $5\frac{1}{2}$ and 6 months, who had progressive lymphopenia and finally diminution of all white cells; post-mortem studies showed atrophy or depression of lymphoid tissue throughout the body. In 1953 Donohue,[11] of Toronto, described a similar case.

The patient was a boy $2\frac{1}{2}$ years old who had had chronic tonsillitis for 6 months that had responded poorly to antibiotic and sulphonamide treatment. The child was pyrexial, and the liver and spleen were much enlarged. The white cells numbered 1100 per c.mm. with 92% granulocytes and 8% lymphocytes; the platelets were normal. The bone-marrow showed plenty of granulocytes and erythroblasts; 18% of the cells were lymphocytes—not a pathologically low figure. Despite blood-transfusion the child's condition steadily deteriorated; the white cells fell to 400 per c.mm., and he died 20 days after admission to hospital. Postmortem examination revealed complete absence of lymphoid tissue throughout the body; the spleen contained no malpighian bodies, and their place was occupied by necrotic tissue and nuclear debris; the lymph-glands were almost devoid of lymphocytes and presented a "sponge-like" appearance: the bone-marrow was somewhat hypoplastic, but all cells except lymphocytes were present; the liver, surprisingly, showed only some congestion to account for its size.

These cases emphasise that absence of lymphocytes is dangerous. This fact has been well known to radiotherapists for years, and the recent experiments with whole-body irradiation preceding marrow grafts have shown again how destruction of lymphoid tissue may render a patient incapable of response to the assaults of outside antigens and infections.

On p. 1123 of this issue Dr. de Vaal and Dr. Seynhaeve, of Amsterdam, report two instances of the most severe of these syndromes—complete absence of leucocytes, both granulocytes and lymphocytes. The patients were male twins born 6 weeks prematurely to apparently healthy parents. Examination of their blood on the day after birth showed complete absence of white cells; the red cells were normal; the hæmoglobin was 110%; and the platelets were normal. Transfused leucocytes disappeared from the circulation within 15 minutes. Despite treatment with penicillin and γ-globulin, the twins died in a septic condition, 5 and 8 days after birth. Postmortem examination showed complete absence of lymphoid tissue throughout the body; the bone-marrow contained no granulocytes or even myeloblasts, but erythroblasts and megakaryocytes were present normally. de Vaal and Seynhaeve name this condition "reticular dysgenesia" because it presumably represents failure of the primitive reticulum cells to produce the cells that develop into the granulocyte, lymphocyte, and monocyte series of cells while continuing to form erythroblasts and megakaryocytes. Their alternative name—"congenital aleukia"—is perhaps more descriptive and brings it into line with the other syndromes of this type.

A blood-count is nowadays a regular part of the investigation of any unusual condition in children; so further cases of this syndrome may be reported. Evidently life without white blood-cells cannot continue for long. Chronic neutropenia is different in that granulocytes are formed in the marrow even though there are few in the blood.

5. Burn, M. Mr. Lyward's Answer. London, 1956.
6. See *News Chronicle*, Jan. 13, 1959; *Lancet*, 1951, i, 102.
7. *News Chronicle*, Sept. 5, 1959.
8. *Times*, Dec. 19, 1958.
9. Wintrobe, M. M. Clinical Hematology; p. 1096. London, 1956.
10. Glanzmann, E., Riniker, P. *Ann. paediat.* 1950, **175**, 1.
11. Donohue, W. L. *Pediatrics*, 1953, **11**, 129.

Special Articles

THE CAUSES AND CURE OF OBESITY

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THE subject of nutrition is one which attracts the crank and the panacea-monger. Everyone is an expert, from the man who swears that there would be no war if we were all vegetarians, to the man who can prevent cancer by making us eat garlic.

Overweight is particularly likely to be the subject of irrationality. This is partly because it is often more obvious than other forms of abnormal nutrition, and partly because it is often a personal problem, affecting ourselves or our relations or friends. On all sides we read and hear about slimming. On all sides we are told of a variety of fantastic and contradictory cures.

It is not surprising that the layman, and occasionally the doctor, is irrational about the *cures* of overweight, when he is so often irrational about the *causes*. There is no evidence that man is immune from the laws of thermodynamics. In every conceivable way it has been proved that the accumulation of excessive fat follows the intake of excessive calories. Again, when caloric expenditure exeeeds caloric income, the consequent fall in weight is as inevitable as the fall in bank balance when monetary expenditure exceeds monetary income. There are often good psychological reasons which make it difficult for people to accept these facts, but facts they certainly are.

On one level, then, one can say quite simply that the cause of overweight is overeating. But on a more practical and useful level, the important question is what is the cause of overeating. How well we can answer this question will determine how well we can treat overweight.

THE CAUSES OF OVEREATING

We began by making the obvious point, but one often overlooked, which is that most people are not overweight. It seems fairly certain that the incidence of overweight is increasing in this and other developed countries. The chief medical officer of the Ministry of Education has recently commented on the increasing number of fat children.[1] It has been said that in the United States as many as 30% of the middle-aged men and women are significantly overweight.[2] But, even so, most people are not overweight. Since in such countries as Great Britain and the United States economic reasons are now relatively rarely the cause of restricted food consumption, and the majority of people can eat as much as they wish, it follows that there must be some mechanism in the normal individual which relates his food intake to his caloric needs. Such a mechanism is the appetite centre in the hypothalmus, which Joliffe [3] has so graphically called the " appestat ".

The appestat reacts to a shortage of calories in some way so as to promote hunger and cause a desire for food. When enough food is taken, the effect upon the appestat is such as to induce the sensation of satiety. For most adults and at most times, the result is that, over periods of a few days at most, caloric intake exactly matches caloric output, and the body-weight remains constant.[4] In children the balance is so set that there are enough surplus calories to determine optimal growth without the deposition of excessive fat.

The appestat reacts primarily to an intake of food. It is, however, still not certain how this information is transmitted to the appestat. Various mechanisms have been proposed—chemical, nervous, and thermal. Thus, Mayer's glucostatic theory suggests that the appestat responds to what one may call the glucose " potential "—that is, the difference in the level between arterial and venous blood.[5] When this is high—for example, after a meal—then hunger is suppressed. When it is low, hunger develops.

Nervous stimuli may come from contractions of the empty stomach, or from the presence of food in the stomach. The former may be associated with hunger, the latter with satiety. The present tendency is to believe that these factors have little if any effect in determining the food intake. But I shall have more to say of this later.

It has been suggested that the appestat reacts to the heat developed by the specific dynamic action of food.[6] We shall need much more information before we can decide whether this is so, and what part it plays. At present, we can only say that we do not know how the intake of food causes its effect on the appestat.

The appestat can be affected by a variety of secondary factors, as well as by the primary ones of the degree of hunger or satiety. I propose to deal with the most important of these factors, some briefly and some in more detail.

FACTORS AFFECTING APPETITE

Genetics

The likelihood of becoming overweight is much greater in someone whose parents are also overweight. The chances of a child being overweight are 75% if both parents are overweight, but only 9% if neither of the parents are overweight. Possibly the setting of the appestat at an abnormally high level is an inherited characteristic. It is, however, also possible that the child learning its eating habits from its parents simply accustoms itself to an abnormally high intake of food. Here is another of those many situations in which it is not possible to distinguish easily between nature and nurture.

Hormones

Deficient secretion of the thyroid or pituitary gland can occasionally give rise to excessive deposition of fat. Here the output of calories is reduced, but this is not accompanied by the equivalent reduction of the intake of calories. The appestat setting, that is, does not become adequately adjusted to the alteration.

This simple concept, however, often leads to two irrational beliefs. The first is that many individuals who are overweight suffer from some glandular dysfunction. Yet in the great majority of obese patients there is no evidence of any endocrine disorder. The second irrational belief is that, if the obesity is due to glandular deficiency, the only way to treat it is by the administration of the appropriate hormone. In fact, it often turns out that the induction of weight-loss by dietary means alone not only cures the obesity but lessens, and often cures, the other signs of glandular insufficiency. The supply of the hormone may now be adequate for a smaller body.

Drugs

Like the other centres in the central nervous system, the appestat may be affected by drugs with a moderately specific action. The best known is dexamphetamine; a

1. The Health of the School Child. Report of the Chief Medical Officer of the Ministry of Education. H.M. Stationery Office, 1958.
2. Hundley, J. M. *in* Weight Control. Iowa State College Press, U.S.A., 1955.
3. Jolliffe, N. Reduce and Stay Reduced. London, 1956.
4. Edholm, O. G., Fletcher, J. G., Widdowson, E. M., McCance, R. A. *Brit. J. Nutr.* 1955, **9**, 286.
5. Mayer, J. *Physiol. Rev.* 1953, **33**, 472.
6. Brobeck, J. R. *Yale J. Biol. Med.* **20**, 545.

newer one is 2-phenyl-3-methyl-tetrahydro-1, phenmetrazine (' Preludin '). Their chief action is to inhibit appetite, but they have various other effects which may preclude their use in particular individuals. When they are used, particular attention should be given to the nutritive value of the reduced food intake.

When drugs are not used, it is usual, but not inevitable, that a diet is prescribed which restricts calories but which ensures adequate intake of nutrients. But when drugs are used, dietary advice is often not given. Since the original diet of the patient may have been unsatisfactory in its content of nutrients, the effect of inhibiting appetite may well be to reduce still further the nutritive value of the diet. One should never prescribe appetite-reducing drugs without at the same time prescribing a diet.

Exercise

It is often pointed out that the 1500 or so calories which may be consumed at a banquet would need, for their expenditure, a walk of about 20 miles or swimming for three hours or cycling for six hours. Statements of this sort, however, are not relevant to the discussion of the factors affecting the appestat. In ordinary circumstances the appestat simply regulates caloric intake in relation to caloric expenditure. When physical activity and so caloric expenditure increase or decrease, food intake increases or decreases in proportion. But this relationship breaks down when physical activity is very low.[7] People who lead very sedentary lives do not always reduce the caloric intake in proportion to their low caloric requirements, and as a result they tend to become overweight.[8] This is no doubt one of the reasons for the increase in weight of many professional people at middle age, when they begin to find that their commitments allow them less and less time for physical activity. It is also one of the reasons for the current increase in incidence of overweight, as progressively our work and our entertainment demand less and less physical activity. Labour-saving devices, mechanisation, motor-cars, and television are examples of factors which, as Passmore [9] has suggested, begin to make *Homo sedentarius* the appropriate name for our species.

Social Factors

There are many occasions when we eat because it is expected of us, rather than because we want to. The expense-account lunch, the cocktail party, the snacks or drinks at the club—these occasions affect more and more of us more and more frequently. Possibly some of us compensate for the excessive calories consumed on one such occasion by eating less the next day. But if the occasions are frequent, adequate compensation becomes less likely. Again, whilst none of us individually will admit to being influenced by advertisements, the manufacturer knows quite certainly that advertising pays. More money is spent on the advertising of foods and drinks than on any other single group of articles.

Psychological Factors

Psychological factors undoubtedly play a part in causing overweight. Most of us have seen patients who have suddenly put on a great deal of weight after some severe emotional experience. In a less dramatic way many people react to stress, anxiety, frustration, and insecurity by overeating. I believe, however, that there are two quite separate unconscious motives for such overeating. For some people, it is an attempt, very roughly, to make up for insufficient love by excessive food. The subsequent overweight is accidental and unwanted, and often a source of great distress. For other people the primary unconscious need is to be overweight. It is the feeling of largeness itself which compensates for the feeling of inferiority. Here, the overeating is only the necessary means of achieving size.

If this argument is accepted, then the appropriate treatment would be different for the two sorts of psychological overweight. In the first group, a diet which would give the same oral satisfaction but fewer calories would lead to a loss of weight: a result which would be much welcomed by the patient. In the other group, there would be far greater resistance to any treatment which could reduce overweight. It is no doubt this second group which is in the minds of those who have been emphasising that overweight might be the most satisfactory adjustment to their problems which some people have achieved, and that weight reduction for such people is not necessarily desirable.

I do not believe, however, that psychological reasons are responsible for most cases of overweight. I do not believe that I and my contemporaries in the forties, who find that we are twenty or even fifty pounds heavier than we were twenty years ago, can get back our former figures only with the aid of psychotherapy. Like the theory of a metabolic defect, the theory that all obesity is due to psychological causes seems to me often to be an attempt to avoid admitting that many of us are lazy and greedy. I should welcome a psychological study of those who so fanatically cling to any single simple cause of obesity, such as metabolic defect or psychological maladjustment.

DOES THE APPESTAT CONTROL ONLY CALORIES?

In all discussions on the appestat, it is implied that this regulates, not the intake of protein or of fat or of carbohydrate, but the intake of calories. " Satiety " implies the satisfaction of the body's needs for calories rather than for nutrients. I have suggested elsewhere that there is probably in fact a specific satiety for particular foods or types of foods, and that this may be important in determining appropriate choice of foods for nutritional needs.[10] But current discussions speak of satiety and of appestat in terms of calories. Even when satiety is supposed to be mediated by the level of glucose in the blood, it is often implied that, calorie for calorie, protein and fat and carbohydrate all affect the level to the same extent. Some commercial interests have nevertheless interpreted the glucostatic theory as meaning that carbohydrate, by raising the blood-sugar more directly, is more satiating than fat or protein; in this way, for example, glucose before meals would result in lower appetite and so there would be less food eaten and a loss of weight.

I have carried out a trial in which overweight men and women were placed on a conventional low-fat low-calorie diet, with or without glucose before meals. At the end of six weeks, those on glucose had lost an average of about $6^1/_2$ lb.; those who were not taking the glucose had lost an average of about $11^1/_2$ lb. (table 1). This difference of nearly 5 lb. is most interesting. The glucose did not decrease appetite sufficiently to cause a greater loss of weight than in the control group. Nor did it merely cause a decrease in the intake of other food to compensate for the glucose, for if this had been so the loss of weight would have been the same as that of the control group. Nor did it cause a lesser loss of weight owing to the extra calories supplied by the glucose, for this would have meant a difference of just over 1 lb. between the control group and

7. Mayer, J., Marshall, N. B., Vitale, J. J., Christensen, J. H., Mashayeki, M. B., Stare, F. J. *Amer. J. Physiol.* 1954, **177**, 544.
8. Mayer, J., Roy, P., Mitra, P. M. *Amer. J. clin. Nutr.* 1956, **4**, 169.
9. Passmore, R. *Proc. nutr. Soc.* 1956, **15**, 83.
10. Yudkin, J. *Lancet*, 1956, i, 645.

TABLE I—LOSS OF WEIGHT OF WOMEN RECEIVING CONVENTIONAL REDUCING DIET, WITH OR WITHOUT GLUCOSE

Group	No. of subjects	Weight loss (lb.)	
		Amount	S.E.
Experimental	18	6·7	1·01
Control	12	11·4	1·34

t=2·80; p=0·01.

that taking glucose, instead of the 5 lb. or so which occurred. So it looks as if glucose has the property of stimulating appetite, and it might then help to put on weight.

I have carried out another experiment which also suggests that appetite is not a simple function of calories. I have put overweight women on the diet which I have described elsewhere.[11] This allows unlimited fat and protein, but severely limits the carbohydrate. Patients may thus eat their fill of such foods as meat, fish, eggs, cheese, butter, and cream. Half were given a preparation of methyl cellulose a short time before their meals. At the end of six weeks the subjects on the diet had lost 6 lb.; those taking the preparation in addition lost nearly 10 lb. (table II). So it looks as if methyl cellulose can really diminish appetite sufficiently to reduce food intake and encourage loss of weight. It is clearly not possible to explain this on the basis of caloric satiety. It does, however, imply that nervous impulses from a full stomach can affect the appestat.

TABLE II—LOSS OF WEIGHT OF WOMEN RECEIVING LOW-CARBOHYDRATE REDUCING DIET, WITH OR WITHOUT A METHYL CELLULOSE PREPARATION ('FORMULA 21')

Group	No. of subjects	Weight loss (lb.)	
		Amount	S.E.
Experimental	10	9·8	1·44
Control	10	6·1	1·10

t=1·99; p=0·05.

FALLACY OF THE METABOLIC DEFECT

In spite of all the evidence that weight increase or decrease comes from caloric imbalance, some people find it extremely difficult to accept. Let us consider the current example of an unsubstantiated theory being used to prop up an irrational explanation of a non-existent phenomenon.

It is suggested that some people have a defect in carbohydrate metabolism involving a block at the stage of pyruvic acid; the pyruvic acid is then diverted to the synthesis of fat. Such people consequently put on fat when eating carbohydrate. But normal people, according to the theory, merely step up their metabolism when eating carbohydrate so that they do not get fat however much they eat.

That is the theory. But the facts are these:

First, there is no evidence that overweight people cannot oxidise pyruvate. Second, there is only one known condition in which carbohydrate metabolism is blocked at the stage of pyruvic acid, and that is beriberi; this disease is certainly not characterised by obesity. Third, and most important of all, it is simply not true that most people—or any single person—can eat more food or less food without changing weight.

In civilised societies, there are always people, who, beginning at the age of 25 or 30 slowly put on 10–20 lb. or more. Must we assume that their ability to oxidise pyruvate becomes abnormal at this time? Again, for the past few decades there has been an increase in the number of people who are overweight. This seems to occur at all ages, and attention has recently been drawn to the increase in the number of overweight children. Are we to suppose that there is an increasing incidence of the metabolic disease which leads to obesity? Is it not more reasonable to ascribe these changes to the twin factors of decreased physical activity and increased consumption of food?

Whatever qualitative difference in metabolism may exist between the obese and the normal individual, we should still not know which was cause and which was effect. Is it the metabolic defect which causes the obesity, or the obesity which causes the metabolic defect? In any event, the important fact is that there is no evidence that obesity is caused by a defect in metabolism. We have signs all around us of how we are becoming more and more sedentary, with motorcars and television and labour-saving devices of all sorts. We have evidence too of the increasing temptation to take calorie-laden foods and drinks, mostly rich in carbohydrate. Why do we need to formulate nebulous and unlikely theories to explain facts which can so readily and simply be explained by existing knowledge?

FALLACY OF "AS MUCH AS I LIKE"

Most lay people and surprisingly many doctors still believe that there are fortunate people whose weight remains unaffected by quite large variations in the amount of food they eat. This is based on two sorts of confusion. In the first, we are told: "Mrs. Smith eats much more than Mrs. Jones, yet she is slimmer". This may well be true. It is then suggested that this proves that Mrs. Smith will not get fat however much she eats. This is false. All it shows is that her total energy expenditure, at rest and at work, is greater than that of Mrs. Jones. Booyens and McCance [12] have shown that there is a great variation in basal metabolic rate and in the expenditure of energy for a given task. One person can thus expend twice as many calories as another without being any more active. It is indeed not surprising that there should be a great individual variation in the efficiency of the conversion of food energy into physical energy, so that there will be great individual variation in food intake. In this mechanical age we must by now be used to the fact that two motorcars may require quite different amounts of fuel. And one does not have to be a mystic to realise that two human beings will show great differences in their biochemical make-up and metabolism.[13]

There is a second sort of confusion which leads people to irrationality on the subject of weight control. This is the confusion between "as much as you like" and "an unlimited amount". This time we are told: "But my cousin can eat as much as he likes, and yet he does not put on an ounce". Let me give an analogy. Before I gave up smoking cigarettes I used to say that I could smoke as much as I liked, yet I never got a smoker's cough. The point was that I smoked an average of fifteen cigarettes a day, never more than twenty. "As much as I like" was in fact still a moderate amount. It would be quite wrong to conclude that I could have smoked fifty or sixty cigarettes a day with impunity. Similarly, the person who eats as much as he likes just does not want to eat more than he can dispose of as energy and heat. He is fortunate enough to have an appetite-regulating centre which is working well. If you could make him eat more, he would put on weight.

We cannot get away from the fact that, given no change in physical activity, increased food means increased weight. Yet this simple expression of the laws of conservation of mass and of energy is still received with indignation by very many people. Two arguments against it are advanced.

11. Yudkin, J. This Slimming Business. London, 1958.

12. Booyens, J., McCance, R. A. *Lancet*, 1957, i, 225.
13. Williams, R. J. Biochemical Individuality. New York, 1956.

In the first, it would be said that experiments such as those of Kekwick and Pawan [14] demonstrated that calories are not the chief factor that determine weight gain or weight loss. These workers have shown that obese patients lose more weight in a week on a calorically restricted diet when it is relatively high in fat than when it is relatively high in protein, or even more so than when it is relatively high in carbohydrate. The most likely explanation of this is that the different diets lead to different degrees of water retention. It is probable, that is, that a continuation of each of the diets for several weeks instead of one week would show that the rates of loss of weight become the same, after the initial differences due to retention of more or of less water. Until we know the results of more prolonged studies along these lines, it is quite illogical, as the authors themselves point out,[15] to extrapolate from these short-term experiments to the lasting effects of changed food habits.

The second argument is that of the clinical anecdote. One will be told of instances where patients have kept to stringent slimming diets but have lost no weight, and of others who have been made to eat more and yet have kept slim. By now several investigations have been reported in which the intake of food has been carefully controlled over a period of several weeks or months. Every one of these shows, unequivocally, that increase in caloric intake leads to increased weight and decrease in caloric intake leads to decreased weight. If we ourselves are unscientific in spite of all the evidence, we must not be surprised if the layman falls for the nonsense of the chiropracter, the woman who runs the slimming clinic, and the "famous American dietitian".

MORE FOOD MEANS MORE WEIGHT

Suppose we make people eat an extra 1000 calories, daily, in addition to their ordinary meals. Suppose too that the calories are derived from protein, fat, and carbohydrate distributed in the same sort of proportion as they are in the ordinary diet. The "anti-calorie" school would suggest that some of these people would be eating these extra calories without decreasing their ordinary food, and yet would still not gain weight. These are the people, they say, who can eat "as much as they like". Now, exactly this experiment has been carried out [16]; and the results are just what one would expect on a straightforward calorie basis. Some of the subjects did in fact eat the extra calories without much decrease in their other foods; they put on up to 10 lb. in eight weeks of extra feeding. Some of the subjects reduced their other food by almost exactly the thousand calories they were getting as an extra; these put on almost no weight. So there are differences between individuals—not qualitative differences in the way they metabolise their food, but quantitative differences in the way their appetite is affected by food.

CONCLUSION

We can thus explain the causes of obesity in terms of a variety of factors acting on the appetite centre so as to cause excessive eating. The two commonest of these factors seem to be: (1) very low physical activity; and (2) the temptation to eat too much, especially of sweet prepared food. Rational treatment of those who really desire to lose weight must also be aimed at affecting the appetite centre, so as to cause decreased eating. The chief aims of treatment will thus be to increase physical activity, and to give a diet designed to be lower in calories while still of optimal satiety. This in practice means a diet which need be restricted only in carbohydrate. As a help in the early stages, when the new dietary habits are being acquired, it may be found useful to take methyl cellulose or possibly some other preparation which decreases appetite.

14. Kekwick, A., Pawan, G. L. S. *Lancet*, 1956, ii, 155.
15. Kekwick, A., Pawan, G. L. S. *ibid.* 1958, ii, 908.
16. Fryer, J. H. *Amer. J. clin. Nutr.* 1958, **6**, 354.

Personal Papers

POST-RADIATION MOUTH BLINDNESS

ETHNA M. MACCARTHY-LEVENTHAL*
M.A., M.D. Dubl.

Sir Ernest Kennaway's account [1] of his reactions as a patient has led me to record my own observations as doctor, patient, and housewife (i.e., cook). I have been treated by radiotherapy for cancer of the pharynx in several hospitals. Nothing could exceed their kindness and clinical care, but all of them lacked understanding of the patient's problems about "food" as distinct from "diet".

Normal taste registers only salt, sugar, acid, and bitter; so where the taste-buds are destroyed, as in radiation, it registers no information. What is it like to lose your sense of taste? To know that the most luscious fruit is a cinder, and its juice an acid liquid flavoured with bicarbonate of soda or copper, or that a Whitstable oyster is no more appetising than a slug?

Imagine having taken a large dose of atropine and then being presented with a piled-high plate of charcoal biscuits by a menacing giant who says "Eat it up, it will do you good". The stomach is now the master and refuses to cope with it, so your œsophagus remains rigid, your pylorus closed. If, by a mighty effort, the "cinders" are forced down with copious fluid, the consequences are acute indigestion or vomiting. The patient is not hungry anyway, and it is easier to starve.

It is difficult to explain to other people this "blindness of the mouth". They can bandage their eyes, but they find it hard to imagine the disgust and suspicion engendered by a "cindery bolus" in the blind mouth. Those faithful sentries, the taste-buds, are dead. The puzzled tongue rejects it, but is too dry to spit it out. And if there is anything objectionable to feel (such as gristle in mince) a sort of panic nausea may be the next reaction. Exhaustion and despair set in, and the already debilitated patient feels that it is all not worth while.

Liquids, on the other hand, have "hallucinatory" tastes. My own is bicarbonate of soda; others taste copper. Each seems to be individual and very real. Why this should be is a question for the biochemist or neurologist. Possibly it is due to a personal fungus infection. This hallucination haunts all liquids, including alcohol. Increasing the strength of alcohol and condiments, such as chutney and pepper, only add a sensation of burning.

To heighten the flavour or condiment is as senseless as shouting at a stone-deaf man. What should be done, if the patient has a sense of smell left, is to use it to stimulate appetite. The soothing aroma will pacify the anxious stomach.

The question is: what smell does he like? If the aroma is not agreeable, the food should be removed at once. No-one should persuade a patient to eat or be cross with him for not eating. It is the kitchen that is at fault. His failure to eat only makes the patient more depressed. Everything must be scalding hot, as only steam can be smelled. This reassures the stomach. The patient will learn by touch when he can safely swallow it. Once the food cools, the savoury aroma has gone, it reverts to "cinders".

The stomach is curiously unsuspicious of anything liquid. Perhaps because of the physiological urgency of thirst, which

* Dr. MacCarthy-Leventhal died on May 24, 1959.

1. Kennaway, E. *Brit. med. J.* 1957, ii, 1485.

bypasses the taste-buds, as compared with the slower mastication of hunger. For this reason, supplementary feeding is easy. A cocktail of glucose vitamins in liquid form will be accepted. Vitamin drops, by their unpleasant penetrating aromatic quality, annoy the bitterly disappointed mouth, but the stomach will accept them.

I offer the following hints for the preparation of meals for the mouth-blind patient:

1. An intelligent and versatile cook is required.
2. Service should not emphasise the patient's difference from the intact. He already feels like a leper and meals should, as far as possible, look normal.
3. It is better to serve small portions often, since once they lose their savoury steam they become as " cinders ".
4. Sweets need ingenuity, because the hottest sugar has no smell. But chocolate and other sauces, aromatised with vanilla or other essences, will help.
5. A dry mouth makes mastication a labour. Hence the necessity for appetising sauces and gravies. Mince is useful because it can be eaten quickly. The eye also plays its part, and this dish should be carefully decorated with colour —e.g., tomatoes or peas. The practice of " dunking " is helpful; biscuits and the like can be softened in fragrant tea or coffee. The small bulk consumed leads to constipation, but this can be met by giving such substances as ' Iso-gel '.

I am a gourmet and my hobby is cooking. When my husband took me to my favourite Chinese restaurant, it was with ludicrous dismay that I realised that I had lost all sense of taste. Gradually, I have learned that it is useless to reach automatically for sugar or salt. I can still cook by smell. But since sugar and salt have none, my guests have to help themselves to these commodities. I can now watch other people eat oysters, lobster (cold), chocolate, and fruit without envy. I still smoke, because I inhale; it passes the time and makes me feel less alien to the rest of the human race. It is a dry job and so far my stomach has not protested; possibly a mustering of blood-sugar soothes its dim hunger.

Dialogues of Today

POUNDS, SHILLINGS, AND RESEARCH

SOCRATES: Tell me, Eryximachus, what you understand by research.

ERYXIMACHUS: I shall take refuge among the modern philosophers, Socrates, and say that research is what research-workers do.

SOCRATES: And medical research, I suppose, is what medical research-workers do?

ERYXIMACHUS: Of course!

SOCRATES: But already, it seems to me, your modern philosophy has raised a problem. Is a medical research-worker a research-worker in medicine or a medical worker doing research?

ERYXIMACHUS: A research-worker in medicine, surely—who may or may not be a doctor.

SOCRATES: And I suppose a doctor may or may not be a research-worker?

ERYXIMACHUS: Yes.

SOCRATES: How do doctors, then, become research-workers?

ERYXIMACHUS: Usually young doctors who show an interest in research and some talent for it obtain posts in which they can continue to do it.

SOCRATES: And do they then do anything else?

ERYXIMACHUS: Some do research only: others combine it with clinical work. These are almost all holders of university posts.

SOCRATES: And are there many doctors doing research either as their sole occupation or as part of their academic work?

ERYXIMACHUS: No, probably only a few hundred.

SOCRATES: But I suppose there are many doctors in the Health Service who are also medical research-workers?

ERYXIMACHUS: Some doctors in the Health Service no doubt continue to do research if they become interested in it when they are training, but only a most persistent man or woman is likely to overcome the difficulties.

SOCRATES: What are those?

ERYXIMACHUS: In the first place most such research is unpaid. Little money is available to pay for research in the Health Service and its spending is hampered by restrictions. No part-time consultant can be given any security that the Health Service will continue his research grant, even if he gets one; so naturally he prefers consultant sessions which do give him security, and gives up his research. But that is not all. If his research involves anything beyond looking at patients he will have nowhere to do it, for the Health Service provides no accommodation for research in its hospitals.

SOCRATES: It does not surprise me that even medical research-workers should be divided into amateurs and professionals, for I know, Eryximachus, that that distinction is one of the foundations of your society; but only in medical research, surely, is the amateur fined for not being a professional.

ENTHUSIASTICUS: Things are not quite as unfair as that, Socrates; for both amateur and professional are penalised for doing research—the amateur by not being paid for it and the professional by being paid much less than his clinical colleague earns by not doing it.

SOCRATES: It seems to me that doctors in this country think research of little value.

ENTHUSIASTICUS: On the contrary they take a great pride in anyone who, in spite of all these obstacles, makes an outstanding contribution to medical knowledge.

SOCRATES: Why, then, do they not encourage more people to do so?

ENTHUSIASTICUS: The reasons are complex and spring partly from history and the national character, which perhaps are two aspects of the same thing, and partly from the organisation of the Health Service. Historically, research and academic medicine have been mainly whole-time work. Anything else has come to be regarded as simply not Goodenough. Consequently the whole-timers have become a kind of medical clergy while the rest of the consultants are the laity, and the two have come to look upon each other as clergy and laity will. The clergy are thought to regard themselves as a purer type of being, which of course is quite unjust, while the laity pride themselves that in contrast they do know more of the world. And this strange dichotomy has spread till whole-time doctors who have no contact with either research or academic medicine are still regarded by their part-time colleagues as members of a sort of lay order. Of course this is the kind of thing administrative technicians batten on; so whole-timers and part-timers are treated differently in every possible way, even to the extent of a distinction between whole-timers and maximum part-timers which carries all kinds of economic consequences. Incidentally this satisfies our national love of class distinctions, with the unusual added advantage that it enables each class to feel superior to the other.

So we have what you have heard, research-workers with their collars the wrong way round, while the great Health Service marches on paying about as much attention to them as the world does to the Church. There is no career in the Health Service for a part-time consultant who wants to combine research with clinical medicine, and time spent on research is time wasted if you want a clinical appointment.

SOCRATES: I think, Eryximachus, that when you said that research is what research-workers do, you were throwing more light upon the truth than perhaps you knew. For every doctor who asks what he can do for his patients is asking many questions which only research can answer, and which in the long run will be answered only if the mind of Medicine is not divided into those who ask the questions and those who try to answer them.

In England Now

A Running Commentary by Peripatetic Correspondents

SOME of my friends seem to think that low I-Q patients must be one of the hardships of general practice. But for me, the slower-witted ones comes as balm to the tired mind, a lull in the remorseless doctor-patient strife. There is never that uneasy feeling that as you try to sum up the patient the converse is also going on. How much hearing time will satisfy them? How much of a "thorough examination" are they determined to have? These questions do not arise. If they do happen to ask "Why is it?" or "Where could such a thing have come from?" any explanation will be accepted with respect and thanks.

I have in mind one Dickie Parkin, one of my favourite patients. When I first met him he was forty years old, a bachelor, and heading straight downhill. He lived alone in a house untouched by brush, cloth, or broom. His lonely meals of bread, jam, and tea were taken from a table spread with last Saturday's *Sports Pink*. On weekend nights he went to the pub down the road and drank half his week's wages. Then he came to know an elderly eccentric widow. He began by occasionally digging over her garden; then he moved in as lodger. A touching and innocent symbiosis was effected. Dickie was a changed man. The old lady kept most of his money, giving him only enough for bus fares and 20 cigarettes a week. She dedicated herself to keeping him clean and smart. She fed him well, staying up until after ten o'clock at night preparing his packed meals for the next day. She went to see him fitted out with two suits, two thicknesses of underwear, even a bowler hat for Sunday. They take the little dog, and go out walks together on summer evenings.

Dickie comes in to see me at the end of the evening surgery; any later-comers gladly accept his offer of an earlier turn. He talks away to the others in a loud, wheezy voice, appealing to each in turn until even the most reserved are engaged in easy conversation. Before leaving the waiting-room, Dickie turns off the light and the gas radiator (which I have to light again). He always brings a bag of peppermints for my wife, bought at a certain stall in the market at a certain time on a Friday evening. He inquires after my children, one at a time by name. Slapping down his shilling on the top of my desk, as if on the counter of a shop, he follows me into the dispensary to see me tip his ephedrine tablets into a box. Then, buttoning up his tailored overcoat and pulling his spotless check cap well down over his eyes, he says "Look after yourself", and is gone with a rush. The thud of the shutting surgery door sets the bottles dancing on the shelf.

* * *

A medical meeting at Norwich took me back to my native Norfolk, to the house where I was born, to the farm where I spent my youth at the beginning of the century. Driving to Norwich, 28 miles away, in a pony and trap was an adventure, taking a little over two hours. Farm labourers were getting 13*s*. a week with few extras, except the harvest money of £7 10*s*. Team men who came early every morning to yoke the horses and stayed longer to feed them and tend them on Sunday got another 3*s*. One of my early political memories was when I was eleven hearing their agreeing, unanimously, that Lloyd George's health insurance scheme was rotten and another example of the healthy rustic being milched for the benefit of the urban rich whose health was poor.

* * *

Passed from hand to hand, your correspondent's preliminary report on the United States has been greeted by "Oh, why didn't he *tell* us he wanted to see chipmunks!" Even my wife conformed to the pattern.

At our country home our dining-room looks out on a stone terrace. Mortar between the stones has, here and there, disappeared, and chipmunks nest conveniently beneath the stones. Last year's family afforded us much amusement, as they chased each other wildly around and around the terrace. They were attracted by the seeds which dropped from the various bird-feeders I had strung up on a pole. The family seemed to number six or seven, and while they chased each other around, they never chased each other off the terrace. That was done only to foreign chipmunks who invaded the territory. One day only one chipmunk appeared. She (or he?) stood up and chattered her teeth for minute after minute, only stopping when a human being came too close. This went on for several hours. Stepping down to a lower grassy terrace, I spotted a large black snake resting drowsily in the sun, evidently recuperating after a heavy meal. Did the several lumps which marred his symmetry mark the immolation of our chipmunk's family?

We never saw that family again, but this year a new family has taken possession of the home beneath the stones. They spend their time eating bird seed, chasing each other, attacking foreign chipmunks, and viewing the scenery. One or more are almost always to be seen standing up at the edge of the terrace observing all that goes on below them. Everyone remarks on the beauty of our view, but the admiration of the chipmunks is the ultimate testimony. Chipmunks feed like rhesus monkeys, paying no attention to their state of repletion, but storing food in their jowls for future use, storage, or burial. Their heads become so heavy that they can barely lift them. These chipmunks apparently live in the ground, using any old hole, and I think they may be the cousins of the ground squirrels which carry the plague in the West. This year, the day after my wife had planted a large number of Dutch flowering bulbs, we surveyed the garden, thinking with satisfaction, "that is one chore done for the season". To our consternation, every bulb had been dug up, the core eaten, and the husk left outside the hole—mute witness to the crime. We never caught the chipmunk in the act, but the circumstantial evidence is overwhelming.

* * *

Autogeriatology,[1] or the study of advancing age in oneself, has been unduly neglected by medical authors. I am about to make a corner in the more interesting physical signs to be noted, though I have expressly forbidden any eponymous association.

The common sign of antiscotopia, or the sudden appearance of an unknown middle-aged face in the shaving-mirror, is well known, as is suprachoreophrasia, or the sudden tendency of the residents to call you sir instead of Charlie. Less commonly noted is dysenantiomorphism, or finding that the mentally noted "damned attractive woman" in outpatients is of an age previously only associated with one's mother. Yesterday, however, I found a new one as yet unnamed. Walking along the main corridor deep in thought, I suddenly noted that I had done up all the buttons on my white coat.

* * *

THE WORM THAT SAID POOH, POOH!

Alas!
I am a worm
My soul cannot attain
The indispensable escape velocity
And so
Uncouth and earthbound
I remain. Men say
They do this miracle or that; the birds
Have whispered to me and I know
The sun no longer shines
It gives off particles and rays—quite cc'd,
For men make imitations now;
The stars are chipped and some require replacement;
And if at night I venture out
I am no longer certain which are real and doubt
Upsets my navigation.
Great news they make, these men,
And yet
They haven't made much difference to the earth
It tastes the same so far
And I remain
Their faithful servant in or on it
Lumbricus *var.*
Sapiens.

1. Eisberger, Hamberger, Sellyberger, *Icelandic J. Proptosis*, 1957, **1**, 2.

Letters to the Editor

REDRESS FOR WRONGED PATIENTS

SIR,—One of my patients, rather a nice chap, has just complained about me, in writing, to my employers. His letter was addressed, quaintly but not inappropriately, to "The General Manager, Ministry of Health", and dwelt at some length—and with a certain eloquence—on my shortcomings.

His main complaint was that I had suggested he might be exaggerating the effects of an injury he had received at work. I will not weary you with the details of our controversy, but it raises an issue which I think is important.

Our patients who suffer injuries which they believe have resulted from the negligence of others, are tempted, on an ever-increasing scale, to seek legal redress. They do not realise that they have embarked on a course which, under our present system, may well leave them not only penniless, but crippled in mind and body.

Some years ago I operated on two men who had widely different outlooks on life. The first had received a severe injury to his left forearm, and when the wounds were healed his hand was pretty useless. He was easily persuaded that he could never work again and, living on public assistance, he devoted his energies to the pursuit of financial recompense. *Five years later* he lost his case in the courts.

The second man, an Irish labourer, suffered a partial avulsion of his right arm, which had to be amputated near the shoulder. No litigation ensued, but in six weeks he had been accepted at a rehabilitation centre, where he learned the trade of oxy-acetylene welding. A few months later, as a skilled workman, he was earning a higher wage than ever before.

Very few of us have characters so strong and resilient that we could remain unaffected by the ponderous tempo of civil legal machinery. Slowly but surely this will grind away the last remnants of dignity, humour, honesty, and self-respect.

Should we not press for the reform of this merciless system? Patients complain to their Members of Parliament if they are kept waiting an hour in the outpatient department, or three months to have their tonsils out. If they have committed a crime, retribution is swift . . . but if they have been wronged, they may wait three, four, or five years for justice to be done. And they have no redress, for Justice is above the Law.

Barnet General Hospital,
Barnet, Herts. V. J. DOWNIE.

TOLBUTAMIDE IN THE TREATMENT OF ANGINA PECTORIS

SIR,—In March, 1957, during the treatment of diabetes mellitus with tolbutamide, it was observed that anginal pain present in 1 case progressively diminished in severity and frequency of attacks until, in about 10 months, it completely ceased to trouble the patient. This had not been noted previously under insulin treatment. Subsequently a nondiabetic patient was also found to benefit from tolbutamide. This observation was a bit too striking to be ignored. Since then we have treated 24 cases of established angina pectoris, and, between us, have been able to confirm the initial observations independently. The patients were specially selected. Nearly all were breadwinners with minimum psychological overlay which might otherwise have interfered in the assessment of results. Others had physical signs, an improvement in which lent some credence to the results obtained.

The patients were 21 men and 3 women (9 diabetics and 15 non-diabetics), 45 to 63 years old; and the duration of their complaint was 2 to 9 years. In 5 cases the complaint was entirely subjective and the frequency of the attacks varied from 3 to 12 times a day. In 14 cases the pain was associated with severe restriction of physical effort; in 5 of these, the electrocardiogram had shown persistent ischæmic changes, and 2 were subject to attacks of cardiac asthma. 5 cases were of post-infarction anginal pain. 17 patients had mild to moderate hypertension. In 3 there was a history of temporary increase in the severity and frequency of anginal attacks after large doses of testosterone.

Although the patients had all been fully investigated before, their latest condition was assessed before tolbutamide was given (complete history, detailed clinical and radiological examinations, electrocardiograms, exercise-tolerance tests, and blood for W.R., red count, and hæmoglobin). The patients kept a card to record the frequency, severity, and duration of anginal attacks and their own capacity for physical exertion. They were seen once a month when their electrocardiograms and exercise-tolerance tests were repeated. In 3 cases basal metabolic-rates, and in 7 cases serum-cholesterol levels, were measured before and during tolbutamide therapy.

Tolbutamide was given in a single daily dose of 0·5 g. at bedtime. Because of the slow therapeutic effect of the drug it was not possible to make a quick change from drug to placebo, or vice versa, and the patients became less cooperative. Thus, much as we wanted to carry out a double-blind trial we were forced to modify the procedure and restrict it to the period after the initial success had been obtained with tolbutamide. However, the patients did not know what they were having at any stage. Drug and placebo were contained in identical capsules.

To ensure that at any time the effect of tolbutamide had completely passed off, the placebo was administered for at least 2 months at a stretch, by the "dispenser" in charge of the capsules. No change was made in the existing routine of the patients and they continued to take nitroglycerine as they liked.

The patients first noticed improvement in 2 weeks to 3 months after starting tolbutamide therapy. The anginal pain became less frequent and less severe, and the capacity for physical exertion increased both in duration and intensity. The improvement was progressive and, as far as routine work was concerned, complete in 7 to 12 months. Nitroglycerine was now no longer required. Thus, for example, a patient who, before tolbutamide, could at a slow pace walk barely 75 yards without precordial discomfort or pain can now comfortably walk from his residence to a bus stand, about $^{2}/_{3}$ mile away, at a normal pace carrying with him a suitcase weighing about 22 lb. Now and then when he has to hurry a little to catch the bus he finds that he can do so. Another patient can now comfortably go up a flight of 84 steps in a 4-storeyed building. Formerly he could negotiate about half the distance, and that too only slowly, and the remaining half not without two or three halts and, sometimes, nitroglycerine. The exercise-tolerance tests have shown similar improvement. Attacks of cardiac asthma have ceased in the 2 patients. In 1 of the 5 patients who had persistent ischæmic changes in all electrocardiograms during the past 5 years the findings are now normal. Large doses of testosterone no longer induce anginal pain in patients in whom they previously did.

On discontinuing tolbutamide, symptoms returned in 7 cases after 2 to 7 weeks, but were relieved when tolbutamide was given again.

In diabetics the dose of tolbutamide was not always adequate to control the diabetes completely and the improvement in anginal pain was not directly related to the degree of the hypoglycæmic effect of the drug. There were no side-effects of tolbutamide.

As the mechanism of anginal pain is itself uncertain, it is rather hard to explain convincingly the beneficial effect of tolbutamide. It it is accepted that the "P" principle of Lewis is lactic acid, the benefit may be accounted for by the reduction of blood-lactic-acid by the drug.[1] As

1. Steigerwald, H., Schoffling, K., Pfeiffer, E. F. Experimental and Clinical Studies of the Oral Therapy of Diabetes Mellitus. Frankfurt, 1955.

lactic acid is freely diffusible, the concentration of lactic acid in muscles and interstitial and intracellular fluids is normally regulated by the blood-lactic-acid levels. Thus, if the blood-lactic-acid level is low, the chances of lactic acid accumulating in high concentration in an ischæmic area of the heart muscle, sufficient to cause anginal pain, are less. On the other hand, the blood-lactic-acid may be increased in diabetics even when they are stabilised with insulin.[1] This probably explains why relief from anginal pain did not occur in our original case when he was under treatment with insulin and why the incidence of angina pectoris is so high in this disease. No antithyroid effect was observed in the B.M.R. readings. Serum-cholesterol was appreciably lowered. The return of the electrocardiogram to normal in 1 case, the improvement of the myocardial function in 2 cases of cardiac asthma, and the failure of testosterone to worsen anginal pain which it previously did in 3 cases are noteworthy.

Armed Forces Medical College, Poona, India. INDER SINGH
P. N. BARDHAN.

LOBECTOMY FOR BRONCHIAL CARCINOMA

SIR,—In your issue of Oct. 24 Mr. Belcher, discussing the value of lobectomy in bronchial carcinoma, reports a relatively high survival-rate for adenocarcinoma and a considerably lower survival-rate in cases of squamous and oat-celled tumours. There is a striking difference in the conclusions drawn by the Mayo Clinic group of workers.[1 2] Part of the discrepancies could well be due to differences in classification.

While the term "oat-cell carcinoma" is more or less synonymous with the "small-cell carcinoma" of American workers, there is much less agreement about the classification of some other types. The Mayo Clinic group have a wide category of "large-cell tumours", and many workers believe that these probably represent both undifferentiated squamous carcinomas and adenocarcinomas but that it is often difficult or impossible to tell which it is in a given case. Some workers, on the other hand, place most of these in the squamous group. It is possible that the exclusion of the undifferentiated squamous type by the Mayo Clinic workers has slightly improved the prognosis of their squamous-carcinoma group, while in Dr. Belcher's series the exclusion of the undifferentiated adenocarcinoma type may have contributed to the better prognosis of the adenocarcinoma group.

The discrepancy between these series requires looking into so that classification between different centres can be better standardised if possible. It is more difficult to explain the slightly higher survival-rate of the oat-cell tumours compared with the squamous-cell tumours in Mr. Belcher's series, considering that the Mayo Clinic group found a strikingly worse prognosis in oat-cell compared with squamous carcinomas. The higher operability-rate and resectability-rate of squamous-cell tumours, compared with other histological types, in the Mayo Clinic series agrees with my finding that at Hammersmith Hospital, London, squamous tumours account for a little more than half the surgically removed bronchial carcinomas and oat-cell tumours for only about a sixth, while in necropsy material oat-cell carcinoma accounts for nearly half the total cases and squamous carcinoma for just under a third. This could perhaps be accounted for in part by differences in the difficulty of technical resection dependent on the sites of predilection of the different histological types, but this argument can hardly be substantiated.

Aside from resectability-rates, however, there are discrepancies in the survival-rates of cases actually resected, when different histological types are compared. Mr. Belcher states that the difference in expectation of life between the various cell types is not accounted for by differences in the incidence of nodal involvement and he concludes that the difference in prognosis must be inherent in the tumour. This appears to suggest, in his series, a greater inherent tendency of the squamous tumours to metastasise to distant organs. These conclusions are opposed to those one would draw from the Mayo Clinic figures. It would be most valuable to have the views of the workers concerned on the possible reasons for these conflicting results.

1. McDonald, J. R., McBurney, R. P., Carlisle, J. C., Patton, M. M. *J. thorac. Surg.* 1951, **22**, 62.
2. Moersch, H. J., McDonald, J. R. *Dis. Chest*, 1953, **23**, 621.

Silver Spring, Maryland. J. Z. AZZOPARDI.

THE NEEDLE AND THE SYRINGE

SIR,—The needle and the syringe sometimes serve as instruments of overinvestigation and overtreatment. If other diseases had so striking a sign as jaundice many more needle-induced diseases might be recognised. If the incubation period is long and the signs and symptoms not characteristic, an offending needle could be overlooked as a cause of the patient's disease. We have an archenemy in the staphylococcus stubborn to antibiotics, but less virulent bacteria and viruses could be fortuitously introduced.

Should not all patients on long-term injection treatment have their own syringe and needle, even when the injections are given by the attendant nurse or doctor? Should not patients in a hospital have their personal needle and syringe throughout the length of their stay? Fastidious patients—and we would all of us be fastidious if the dangers were known—should buy a new needle, for personal use only, with each batch of ampoules.

Mayer de Rothschild Hadassah University Hospital, Jerusalem. ELI DAVIS.

OUTBREAK OF POISONING IN MOROCCO

SIR,—We were most interested to read the report of Dr. Honor Smith and Dr. Spalding (Dec. 5) upon their investigation into the outbreak of paralysis in a certain area of Morocco, due to the addition of *ortho*-cresyl phosphate to the olive oil used in cooking.

By the end of November the total number of cases had increased to 10,000 and the Moroccan Government were faced with a great tragedy. Olive oil is one of the principal ingredients of the daily diet of the native population and, while in some cases entire families have been affected, in others the children, although unaffected, are uncared for because the older members cannot look after them.

The Moroccan Government immediately voted a large sum to set up a special hospital at Meknes with treatment centres in the surrounding region. As the number of victims increased, however, it was realised by the Moroccan Government that its national resources would not suffice to cope with the situation and appeals were made to the World Health Organisation and to the League of Red Cross Societies for assistance.

Physiotherapy is urgently needed, to limit the extent of paralysis, to speed recovery, and to prevent physical deformity in severely afflicted patients. The Red Cross Societies of all countries have therefore been asked by the League for assistance—doctors, physiotherapists, as well as hospital supplies. The League hopes also to be able to set up two field hospitals of 400 beds each in rural centres.

The British Red Cross Society decided to send physiotherapists and medical supplies and approached the Chartered Society of Physiotherapy. The Westminster

Hospital most kindly agreed to second two physiotherapists from their staff, and University College Hospital has also most kindly done the same.

These four ladies will be sent almost immediately by the British Red Cross Society to Morocco, as soon as they have been briefed and kitted. They will fly to Casablanca and then go on to Rabat.

Their principal work is likely to be the training of Moroccan personnel—nurses, student nurses, 5th-year medical students, and Moroccan Red Crescent members, while providing treatment for the paralysis victims.

Before they go they will have the advantage of meeting Dr. Honor Smith and Dr. Spalding and of being given the background of the outbreak and advice regarding physiotherapeutic measures.

F. C. HILTON-SERGEANT
London, S.W.1. Medical Adviser, British Red Cross Society.

THE NATURE OF ESSENTIAL HYPERTENSION

SIR,—In reply to Platt: yes, evidently it was a pity. By all means let us dispense with mental righteousness, whether with a positive or negative sign, and consider the problem on its merits.

Oxford. G. W. PICKERING.

TREATMENT OF CEREBRAL FAT-EMBOLISM

SIR,—It is not known whether treatment with heparin is of value in fat-embolism, and the problem will not be solved unless a controlled trial is carried out. The objection to a clinical trial is that heparin might cause hæmorrhage, an argument repeated by Dr. Harnett and his coauthors in their report (Nov. 7) of a patient with cerebral fat-embolism. The objection is valid when large doses of heparin are given, and in most reports of the treatment of fat embolism with heparin, "anticoagulant" doses have been given. For example, Sage and Tudor [1] gave 4000 units intravenously four-hourly in one case and 25,000 units intramuscularly twice daily in another case. Mr. Osborne reported (Nov. 21) that he gave 10,000 units six-hourly (the route of injection was not stated) to a patient he treated successfully.

It does not follow that when heparin is used as an antilipæmic agent it must be given in "anticoagulant" doses. An intravenous injection of as little as 200 units of heparin will produce measurable quantities of clearing-factor. The production of clearing-factor increases with the dose of heparin until there is a maximal response [2] after which any further increase in the dose of heparin will probably produce more prolonged but no greater antilipæmic activity. In treating fat-embolism the aim, obviously, is to devise a scheme of dosage which gives a high clearing-factor production but little anticoagulant effect. 2500 units of heparin given intravenously has little effect on the clotting-time and its action lasts less than an hour.[3] On the other hand there is considerable clearing activity in plasma withdrawn 40 minutes after such a dose, which is probably as near as one can get to the ideal. In the two cases I treated with Mr. C. F. I. Sparling [4] we gave 2000 units intravenously every four hours; but probably 2000 units every two hours would be a safe dose.

The use of heparin as an antilipæmic agent is largely empirical as there are little data on which to base the dosage. There is no standard method for measuring clearing-factor in vitro; each investigator has his own method, and if there is such a thing as a therapeutically adequate concentration of clearing-factor, its level is not known.

However, until a drug such as laminarin sulphate [5] becomes available, heparin, in appropriate dosage, is probably worth a trial in fat-embolism, but it must be stressed that its efficacy is unproved.

The Royal Hospital, Sheffield. HAROLD COHEN.

1. Sage, R. H., Tudor, R. W. *Brit. med. J.* 1958, i, 1160.
2. French, J. E., Robinson, O. S., Florey, H. W. *Quart. J. exp. Physiol.* 1953, **38**, 101.
3. Duff, I. F., Linman, J. W., Birch, R. *Surg. Gynec. Obstet.* 1951, **93**, 343.
4. Cohen, H., Sparling, C. F. I. *Brit. med. J.* 1958, i, 1353.

URINARY INFECTION IN THE NEWBORN

SIR,—Dr. Ursula James (Dec. 5) has written upon an important and very difficult subject. I was so surprised by the frequency of urinary infection in the newborn in her series (1·5% of all deliveries) that I looked up the incidence during one year (1958) in one of the maternity hospitals which I visit. I found there were 17 definite cases in about 2200 deliveries—an incidence of approximately 0·8%. In this hospital there is an equal awareness of the condition and the indications for investigation are apparently identical. The discrepancy in the incidence is almost certainly due to lack of agreement on the criteria for diagnosis, and it is this lack of agreement which makes the subject so difficult.

Dr. James states that the onset in her 32 cases was between the 6th and 12th days, and that none of the babies was wholly bottle-fed at the onset of symptoms. The period she mentions is often a difficult one, especially for the breast-fed baby before lactation is fully established. An underfed baby, particularly if dehydrated, will certainly lose weight and may suffer from anorexia, apathy, fever, and vomiting. I think it also possible that the dehydration may lead to concentration of the urine, increased cell-count, and a raised blood-urea. If sterile urine is obtained in only 4% of healthy neonates, the probability is very great that urinary infection will be diagnosed and therapy begun. At the same time care is taken to ensure an adequate fluid intake, and when the infant rapidly improves one is left wondering whether he would not have done so equally well on fluids alone.

In this paper the suggested diagnostic criterion is a cell-count in uncentrifuged urine of 50 white cells per c.mm. in females and 25 per c.mm. in males. Unfortunately, the pus-cell counts from table I have been omitted, but she quotes one boy among the 100 healthy infants in whom the cell-count reached 125 per c.mm. but fell to 20 after twenty-four hours. This makes me wonder whether it would not be better to repeat the examination in suspected cases after forcing fluids for 12 to 24 hours.

I am grateful to Dr. James for drawing attention to the importance of urinary infection in the newborn. I shall continue to look for the condition in infants who fail to thrive and to adopt my present policy which is: when in doubt, treat. However, if I ever find it necessary to treat an infant for six weeks I shall be very suspicious of an underlying congenital anomaly.

London, N.W.3. R. J. K. BROWN.

BIGGER RUBBER GLOVES WANTED

SIR,—I shall be most grateful if you will allow me space to inquire how many surgeons there may be like myself whose hands do not fit the standard pattern of rubber glove. It is clearly unreasonable to expect manufacturers to make a special glove for one surgeon at a price comparable with standard sizes, but if there are enough people requiring them they might be persuaded to do so.

My particular trouble is that my thumbs are much wider than is allowed for even in the largest size glove (which I require in any case). The result of this is that I get a relative ischæmia of the thumb which causes a

5. Besterman, E. M. M., Evans, J. *ibid.* 1957, i, 310.

persistent tenderness and pain for many hours after an operating-list.

If anyone suffering from this or similar troubles would like to write to me I will try to correlate replies and get in touch with one of the glove manufacturers.

97, London Road,
Gloucester. J. F. BOURDILLON.

MASSIVE ALBUMINURIA FOLLOWING AORTOGRAPHY

SIR,—It has been known for some time that after the intravenous injection of radio-opaque substances the urine gives an apparently "false-positive" result for protein with the salicylsulphonic-acid test.[1] Recently it has been reported that urine containing various radio-opaque substances does not give false positive results with the 'Albustix' test (Ames Co. Ltd.) which is claimed to be more specific for protein.[2 3]

During the clinical trial of a new paper-strip test ('Uristix', Ames) (not available in this country) designed to detect both proteinuria and glucosuria, I found a strongly positive result for protein in the urine of a patient after an aortogram with diodine, the diethanolamine salt of 3,5 diiodo-4-pyridone-N-acetic acid. This result was at first thought to be a false positive due to the excretion products of diodone, but as the protein-testing portion of uristix is similar to albustic, and therefore presumably not likely to give a false positive, I decided to investigate this apparent anomaly.

Samples of urine were tested from each of 24 patients before and after injection in the following groups:

Group A. Aortogram (4 patients: 2 samples before, 2 samples after).

Group B. Intravenous pyelogram (18 patients: 1 sample before, 1 sample after).

Group C. Angiocardiogram (2 patients: 2 samples before, 2 samples after)

The results are summarised in the accompanying table.

RESULTS OF URINE TESTS BEFORE AND AFTER INJECTION

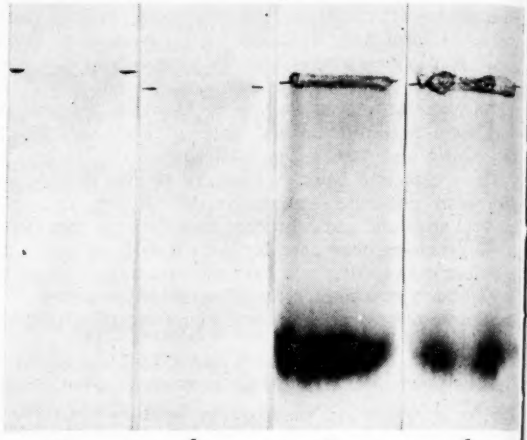
Procedure	No. of cases	Tests for proteinuria	
		Before injection	After injection
A. Aortogram*	4	3 negative 1 trace positive (+)	All 4 strongly positive (+++)
B. Intravenous pyelogram	18	12 negative 6 positive (+)	2 positive (+++) 10 negative (unchanged) 1 positive (increased +++) 4 positive (unchanged) 1 negative
C. Angio-cardiogram	2	2 negative	1 negative 1 positive (+)

* These urines were further examined by electrophoresis.

To confirm the presence of protein, 11 of the urines from group A (aortogram) were further examined by dialysis and subsequent electrophoresis; those taken after aortography all showed the presence of abundant material at the site corresponding to the albumin fraction (see figure). Quantitative values of 730 mg. and 1300 mg. per 100 ml. (i.e., a massive proteinuria) were obtained by the biuret test which is thought to be specific for the -CO-NH-grouping of proteins; the biuret tests against the opaque media in vitro gave values of only 16 mg. for 'Hypaque' (sodium diacetamido triiodobenzoate) (Bayer) and 115 mg. per 100 ml. for diodone.

These results suggest that the intravascular injection of radio-opaque material, particularly into the aorta, may be followed by gross proteinuria. The implication of temporary renal damage is of course obvious, and this is being investigated further.

1. Harrison, G. A. Chemical Methods in Clinical Medicine. London, 1957.
2. Baron, D. N., Newman, F. *Brit. med. J.* 1958, i, 980.
3. Frazer, S. C. *ibid.* p. 981.



a *b* *c* *d*

(*a*) Day before aortogram, no proteinuria.
(*b*) Day of aortogram: before aortogram, no proteinuria.
(*c*) Day of aortogram: after aortogram, gross proteinuria (1300 mg. per 100 ml.).
(*d*) Day after aortogram: gross proteinuria (500 mg. per 100 ml.).

I am grateful to Sister C. A. MacPherson, of the radiology department, for her cooperation and help with the collection of urine samples and to Miss M. R. Haslock, B.SC., of the department of pathology, for technical assistance.

Department of Pathology,
Queen's College,
University of St. Andrews. JAMES A. KIRKLAND.

GASTROINTESTINAL CANCER AND ALBUMIN TURNOVER

SIR,—We read with interest Dr. Madden's observations (Nov. 28) on total exchangeable albumin pool and turnover studies using ^{131}I-albumin on 3 patients with malignant disease and hypoalbuminæmia. 2 of his 3 patients—both with high gastrointestinal cancer—showed high rates of protein (albumin) synthesis despite severe hypoproteinæmia, and as neither of his 2 patients had external protein loss he thinks it would be interesting to speculate on the possibility of internal protein shunts in patients with malignant disease.

Dr. Madden cites a paper by us [1] and states that we believe that if external loss can be ruled out, this indicates internal loss. In this paper, however, we clearly showed in 3 patients with high gastrointestinal cancer (in the stomach) an abnormal permeability of the gastrointestinal tract by means of the ^{131}I-P.V.P. test introduced by Gordon.[2] The 3 patients had hypoproteinæmia and it was also mentioned that one of these patients had free albumin in the gastric juice. We finally expressed our belief that the hypoalbuminæmia often seen in gastric cancer could be caused by a loss in the gastrointestinal tract.

These observations have been extended and confirmed on several patients with cancer of the stomach [3] and we think it is extremely probable that the very low serum-albumin values in Dr. Madden's 2 patients are due to gastrointestinal protein loss. A ^{131}I-P.V.P. test would surely show a gastrointestinal protein leakage in Dr. Madden's 2 patients as it did in ours.

Medical Department B,
Bispebjerg Hospital,
Copenhagen. M. SCHWARTZ
S. JARNUM.

1. Schwartz, M., Jarnum, S. *Lancet*, 1959, i, 327.
2. *ibid.* p. 325.
3. Jarnum, S., Schwartz, M. (in the press).

HIGH-PROTEIN DIETS

SIR,—Dr. Madden (Nov. 28) has fed high-protein diets to cachectic patients and has shown that the 50 or so grammes of nitrogen retained do not appear to contribute to their exchangeable albumin pool. He implies that it therefore does not benefit the patient. He says that the lean-muscle mass "probably varies with the circulating protein mass", but his own paper and other work [1–3] shows that it does not. If the 50 g. nitrogen is neither in plasma-protein nor in body-protein, where is it?

He comments on the very short half-life of albumin in two cachectic patients, for whom curves are not shown. This may in part be because eleven days is barely sufficient time for the estimation of albumin half-life, but it may also be because he is flushing out the tracer with a large protein input which is passing through the albumin pool into the tissues where, perhaps, it is most needed. Dr. Madden will have done a disservice to protein-depleted patients if he persuades us that he has shown that feeding them protein does no good.

R.A.F. Institute of Aviation Medicine, Farnborough, Hants. J. S. GARROW.

USE OF THE TERM "SUPERFEMALE"

SIR,—We have noted with interest the suggestion of Dr. Curt Stern (Dec. 12) that the term "metafemale" should be introduced to describe those human females who possess the karyotype 3X 2A. We found, however, that we were unable to come to unanimous agreement about the full implication of Dr. Stern's letter, inasmuch as we could not decide whether the term "metafemale" was to be applied to female *Drosophila* of the karyotype 3X 2A as well as to those with the karyotype 4X 3A. On the other hand, we are unanimously agreed that Dr. Stern has failed to advance adequate reasons for us to withdraw the term "superfemale", which we have applied to a human female of the karyotype 3X 2A.

It appears from Dr. Stern's letter that, in an as yet unpublished paper, Frost has used "metafemale" to describe a *Drosophila* with the karyotype 4X 3A. It seems unwise to us to broaden this term with the purpose of including the different karyotype 3X 2A, be it a *Drosophila* or human female.

We do not subscribe to Dr. Stern's view that the influence of the X chromosome in human sex determination is unknown; in contrast we believe that there is evidence for the X chromosome possessing a feminising influence. The study of those examples of Turner's syndrome with the karyotype X 2A suggests that the X chromosome is by no means devoid of such an influence. Thus if we regard the phenotype of such patients as essentially that of the neutral basic sex, it can be argued that the addition of a second X chromosome to the karyotype feminises by virtue of its promotion of the normal development of the ovaries and the genitalia. If this argument is granted then we feel that the finding of female breast development in many cases of Klinefelter's syndrome with the karyotype XXY 2A further underlines the feminising influence of the X chromosome. We believe, therefore, that, in a genetic sense, a woman with three X chromosomes is more female than a woman with two X chromosomes. This argument is not invalidated by the fact that, within our very limited experience, the phenotype of the triple X female is apparently less feminine than that of a normally constituted woman. We submit, therefore, that the term "superfemale" remains an eminently proper one.

1. Whipple, G. H., Miller, L. L., Robscheit-Robbins, F. S. *J. exp. Med.* 1947, **85**, 277.
2. Yuile, C. L., Lucas, F. V., Neubecker, R. D., Whipple, G. H. *Fed. Proc.* 1955, **14**, 424.
3. Garrow, J. S. *J. clin. Invest.* 1959, **38**, 1241.

Dr. Stern also suggests that the report of our "superfemale" being of lower than average intelligence is a consequence of her triple X constitution. We would point out, however, that half the women of the world must of necessity be of lower than average intelligence, and that these women are certainly not all "superfemales".

Finally, we do object to the introduction into the English language of a word which is the illegitimate product of a Græco-Roman alliance.

PATRICIA A. JACOBS
A. G. BAIKIE
W. M. COURT BROWN
D. G. HARNDEN
T. N. MACGREGOR
N. MACLEAN.

Medical Research Council Group for Research on the General Effects of Radiation, Western General Hospital, Edinburgh.

ORGANISMS IN UNBLEACHED COTTON-WOOL

SIR,—We were recently asked to examine some disposable babies' napkins which, we believe, are very popular in hospitals and other institutions. The products of two separate firms were submitted to us. In appearance they were similar, each consisting of an inner pad of unbleached cotton-wool enclosed in a gauze mesh. Bacteriological tests were then carried out and all the specimens were found to be harbouring both aerobic and anaerobic organisms.

Readers will recall a circular relating to unbleached cottonwool and its hazards put out by the Ministry of Health.[1] We venture to suggest that its recommendations should not be lightly set aside.

The General Hospital, Birmingham. M. J. MEYNELL.

FOLIC-ACID DEFICIENCY IN PREGNANCY

SIR,—I was interested to read the letter of Dec. 5 from Mr. Francis and Dr. Scott on the routine administration of folic acid and iron to antenatal patients. With this problem in mind, over the past year I have been following two groups of antenatal patients—one receiving ferrous sulphate and the other ferrous sulphate and folic acid.

Venous blood samples were taken at first visit and again about the 32nd week for hæmoglobin and other tests:

	No. of patients	*Average initial Hb*	*Average no. of weeks' treatment*	*Average change in Hb%*	*No. with fall in Hb%*	*5th day postnatal level of Hb*
Ferrous sulphate ..	59	81%	10·4	+1·4	23	80·1%
Ferrous sulphate and folic acid ..	85	77%	10·5	+1·9	28	77·5%

Whether the hæmoglobin change in these cases is of statistical importance or not, from a practical viewpoint the change is negligible.

About half the patients had an initial hæmoglobin under 80%, and 16 were under 70%. At second testing there were 6 who were still no better than 70%. All 6 happened to come from the folic-acid group. Some of these patients admitted to forgetting to take the tablets, but in 2 it was felt that a dietary deficiency of protein was to blame.

The purpose of this letter is not to deny the value of prophylactic treatment which is based on sound theoretical grounds. It is to present some figures and to emphasise the fact that the routine administration of tablets alone will not prevent all anæmia, and that, therefore, repeated hæmoglobin estimations must be made. Curative treatment should then be given as indicated. At all times the importance of a good diet both during and after pregnancy should be stressed.

The Maternity Home, Victoria Park, Warrington, Lancs. C. H. DE BOER.

1. H.M.59(53), May 21, 1959.

TREATMENT OF GALACTOSÆMIA

SIR,—In their letter of Nov. 14 Dr. Payne and his colleagues advocate the use of soya preparations for the treatment of galactosæmic infants on the grounds that no galactose is liberated from the α-galactoside stachyose by incubation with 0·1 *N* HCl or pepsin/HCl and trypsin. No substantial hydrolysis of stachyose would, indeed, be expected under these conditions.

The categorical statement by Armstrong [1] that the tetrasaccharide is not attacked by intestinal enzymes should, in our view, be regarded with caution until the problem has been reinvestigated by up-to-date methods. Much more recently, Clarke et al.[2] investigated the metabolism of melibiose (the simplest α-galactoside), among other sugars, by adult rats and concluded from liver-glycogen determinations that the intestinal tract lacks α-galactosidase. That this lack may be relative is indicated by the fact that melibiose did, at least in some animals, produce a rise in liver glycogen as revealed by analysis 8–9 hours after administration of the sugar. This is clearly a severe test, but the result suggests that galactose *may* be liberated from α-galactosides. We feel, therefore, that it would be prudent to exclude all galactosides from the diet until positive proof has been furnished that they are not hydrolysed by salivary, gastric, pancreatic, mucosal, or bacterial enzymes.

The galactosæmic subject may have a limited capacity to metabolise galactose by the usual or an alternative pathway, but if this capacity is exceeded, galactose-l-phosphate is bound to accumulate. It is now known that galactose-l-phosphate does, indeed, accumulate in most, if not in all, tissues [3] when the diet contains sufficient galactose. Since apparently satisfactory clinical progress does not necessarily exclude the possibility of damage to the developing brain, a galactose-free diet, together with periodic checks on the erythrocyte galactose-l-phosphate as an index of general tissue galactose-l-phosphate, would seem to us reasonable precautions.

The values for erythrocyte galactose-l-phosphate reported by Payne et al. are very much lower than those found by us. In 37 determinations on galactosæmic infants at various ages and stages of treatment the galactose-l-phosphate varied from 7 to 54 μg. per ml. cells.[3]

While the fate of α-galactoside galactose in the intestinal tract is still unknown, we would like to draw attention to the fact that some infants given 'Wanderlac' do not progress satisfactorily, even as judged by short-term clinical criteria. An infant with galactosæmia improved rapidly when put on this soya preparation, but failed to gain weight (see figure). After six weeks, during which he vomited frequently, he had gained only 5 oz., in spite of the addition of rice to the diet 3 weeks after commencing wanderlac. On substituting 'Nutramigen' he gained 1 lb. 13 oz. in the first week, and he has continued to gain weight. We do not consider that the failure to gain weight need necessarily be ascribed to the presence of α-galactoside in the diet, but it is a possibility which should not be overlooked.

In our opinion it is wise to avoid all galactosides until they have been *proved* not to yield even small amounts of free galactose in the intestinal tract.

It is probable that the galactose-l-phosphate content of the erythrocytes will prove to be a more sensitive short-term index of the patient's progress than observation of his clinical condition, and it should be estimated unless the food given has been proved to be safe. It is possible that slight but permanent damage to the developing brain may result from the accumulation of galactose-l-phosphate even when frank symptoms and signs have disappeared.

Departments of Child Health and Pathology, University of Manchester.
V. SCHWARZ
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R. A. GOODELL.

1. Armstrong, E. F. The Simple Carbohydrates and the Glucosides. London, 1919.
2. Clarke, F., Solkot, R., Gorley, R. C. *J. biol. Chem.* 1939, **131**, 135.
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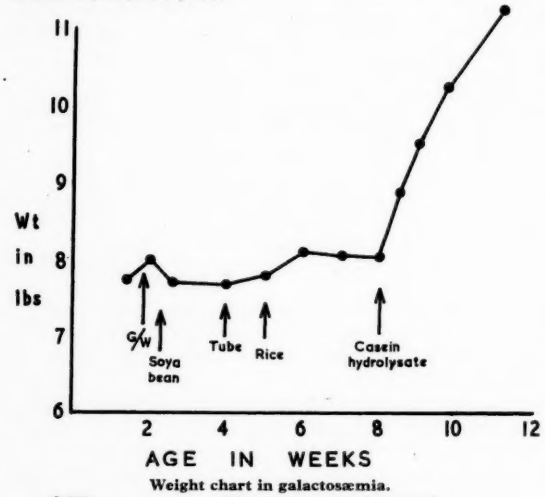


Weight chart in galactosæmia.

G/W	= Glucose-water feeds started.
Soya bean	= Soya bean ('Wanderlac') started.
Tube	= Tube feeds of wanderlac started.
Rice	= Rice supplements started.
Casein hydrolysate	= 'Nutramigen' started.

PETHILORFAN IN LABOUR

SIR,—In the past, there was some reluctance to give adequate doses of pethidine to women in labour for fear of respiratory depression in the baby. It has, however, been claimed that a mixture of pethidine plus an antagonist provides safer obstetric analgesia than does pethidine alone.[1 2] In view of these claims, we decided to evaluate the effectiveness of 'Pethilorfan', a proprietary preparation containing a mixture of pethidine hydrochloride and levallorphan tartrate ('Lorfan') in the proportion of 80 to 1, and to assess its effect on the respiration of the newborn infant.

250 patients in normal labour received pethilorfan, some only half an hour before delivery. The drug was given in divided doses, the total doses ranging from 150 mg. pethidine plus 1·875 mg. levallorphan to 300 mg. pethidine plus 3·75 mg. levallorphan. Chloral hydrate (either gr. 30 by mouth or gr. 60 per rectum) was also given in 85 patients. We found that pethilorfan appears to be slightly inferior to pethidine in analgesic potency, 1·5 ampoules pethilorfan (containing 150 mg. pethidine) being approximately equivalent in analgesic power to 100 mg. of pethidine alone.

For assessing the effect on the infant's respiration, we adopted an arbitrary period of about 4 minutes within which normal respiration should be established. Using this criterion in the 250 deliveries, there was no respiratory depression in the infants that could be attributed to the analgesic and no cases of delayed apnœa.

Pethilorfan was also used in 34 patients in whom a general anæsthetic was required for cæsarean section or forceps extraction. The patient was premedicated with atropine gr. $^1/_{100}$ intravenously. This was followed by intravenous pethilorfan (pethidine 100–150 mg. plus levallorphan tartrate 1·25–1·875 mg.), thiopentone (0·15–0·3 g.) and gallamine ('Flaxedil') (80–100 mg.). Each patient was then intubated with a cuffed endotracheal tube, and assisted respiration was maintained with oxygen (2 litres per min.) and nitrous oxide (6 litres per min.). The results were:

	No. of cases	*Respiratory depression*			
		None	*Moderate*		*Stillborn*
Forceps extraction (25)	..	20	.. 2	..	3
Cæsarean section (9)	..	6	.. 3	..	0

1. Baker, F. J. *Anæsthesia*, 1957, **12**, 282.
2. Lloyd, J. S. *Va med. Mon.* 1956, **83**, 551.

The term "moderate respiratory depression" was used to indicate that a short period was necessary for resuscitation of the baby. 2 of the stillbirths were anencephalic monsters, and in the 3rd death was due to intracranial hæmorrhage.

In both the normal and abnormal labours, the general clinical impression was that pethilorfan is safe for use in obstetrics and produces no neonatal respiratory depression, either immediate or delayed.

Park Hospital,
Davyhulme.

R. L. CUMMING
E. B. GARNER.

FIBROCYSTIC DISEASE OF THE PANCREAS

SIR,—Dr. Roberts (Nov. 28) suggests that "the primary abnormality in fibrocystic disease is persistent overstimulation of the secreting glands". It is difficult to see how this can account for the increased sweat electrolyte concentration, since di Sant'Agnese et al.[1] in fact found that it was not accompanied by an increase in the sweat volume. I should like to suggest that the abnormal sweat electrolyte concentration is due to the absence of the mechanism for reabsorbing salt from the sweat, just as cystinuria, which is also a hereditary recessive disease, is due to the absence of the mechanism for reabsorbing cystine and related aminoacids from the urine.[2]

It has been shown [3] that the relationship between the sodium concentration of the sweat and the sweat-rate can be explained by supposing that sweat is formed from a "precursor fluid" in which salt is present in the same concentration as in serum, and that salt is then reabsorbed from this fluid as it passes down the duct by an active mechanism which has a limiting capacity. This reabsorptive mechanism is controlled by the level of circulating corticosteroids, which explains why the sweat-sodium is the same as the serum-sodium concentration in Addison's disease.

di Sant'Agnese et al.[1] reported that the mean sweat sodium and chloride concentrations in fibrocystics were 133 and 106 mEq. per litre respectively, very close to normal serum levels, compared with 59 and 32 mEq. per litre in controls. Furthermore, there was no decrease in the sweat electrolytes in response to either salt-loss or administration of deoxycortone. This is just what one would expect if the mechanism for reabsorbing salt from the sweat were absent or unable to function.

Unit of Biometry,
University of Oxford.

M. G. BULMER.

WITHHOLDING OF SICKNESS BENEFIT

SIR,—There is a state of affairs concerning payment of sickness benefit which, in my opinion, should be loudly proclaimed and made widely known—namely, that if the medical certificate for the illness is not sent in within a specified time, and a cause for the delay given which is acceptable to the Insurance authorities, then payment is refused. This fact is known to many people already, but by no means all. I discovered it only by being ill and sending in my certificates some months late.

The delay in sending in the certificates was due to a genuine misunderstanding on my part, but my explanation was not enough for the local Insurance office, and payment was immediately refused. This refusal to pay was sent to me on a buff *printed* form, which can only mean that many such forms are sent out. It would be interesting to know exactly how much per annum is saved on such refused claims.

If there has to be a check on the date these certificates are sent in (although, if authentic, why a time limit?), then by all means impose a fine or penalty on the tardy, but to withhold *all* payment for such a reason is to me unreasonable, unjust, and downright dishonest.

Lenham, Kent. W. A. HERVEY.

DIABETIC PETS

SIR,—There must be amongst members of the medical profession some who own diabetic pets. We are interested in the development of certain complications which do not seem to occur in animals rendered diabetic by the usual experimental means, and I should be most grateful if anyone owning, or knowing of, spontaneously diabetic animals, particularly dogs maintained for any length of time on insulin, would get in touch with me.

Medical Unit,
St. Mary's Hospital,
London, W.2. HARRY KEEN.

BLOOD-GROUPS

SIR,—In his response of Nov. 14 to my letter on blood-groups, Dr. Mourant is unable to contradict the facts. Lest these facts be lost sight of, they must be reiterated:

(1) C-D-E protagonists continue to teach triple inheritance of the Rh-Hr factors even though readily available evidence shows that these blood factors are actually transmitted in sets of unequal size containing up to ten or more factors. Moreover, as I have pointed out, the number of factors characterising each agglutinogen is unlimited theoretically, and the number found depends primarily on one's enterprise and ingenuity in searching for and identifying antibodies of new specificities.

(2) The two nomenclatures, Rh-Hr and C-D-E, are not mutually equivalent, so the problem is not simply one of choosing between them, as claimed by C-D-E supporters. This is not the place to repeat once more all the evidence which proves that the C-D-E notations misinterpret and distort the facts, and as a result lead to numerous contradictions and paradoxes.

(3) As for the studies on blood-groups and disease, "the proof of the pudding is in the eating". After the discovery of the Rh factor was announced, Rh-Hr tests were soon incorporated into clinical medicine and this discovery led to tremendous advances in the knowledge of blood-groups, while, in contrast, the reported associations between blood-groups and disease have proved meaningless and found no clinical application, and this type of "research" has led nowhere but is still at the same stage as when it began 30 years ago. Such studies consist merely of a series of disconnected observations which are mutually contradictory, and instead of illuminating the subject lead only to confusion and chaos. Workers 30 years ago did not need R. A. Fisher or E. B. Ford to stimulate or inspire them to carry out similar investigations, and succeeded in producing results equalling those of modern times in meaninglessness.

(4) While protesting against my suggestion that the reported associations between blood-groups and disease may have resulted from some sort of bias in collecting the data, Dr. Mourant himself offers no alternative explanation of why group-O persons should be subject to duodenal ulcers, or why group-A persons should be prone to fracture their femurs, &c. The answer is, of course, that the most difficult things to explain are those which are not true.

(5) The so-called protest signed by "33 leading American workers" stating that the nomenclature problem has to be settled by a "representative committee" must be challenged. Otherwise, why during the three years which have passed since the American Medical Association report was published have those workers failed to take advantage of the numerous opportunities which have presented themselves for the formation of such a committee? Will Dr. Mourant himself give the date and place for the meeting of such an international committee? If not, one must conclude that C-D-E supporters have no inten-

1. di Sant'Agnese, P. A., Darling, R. C., Perera, G. A., Shea, E. *Amer. J. Med.* 1953, **15**, 777.
2. Harris, H. Human Biochemical Genetics. Cambridge, 1959.
3. Bulmer, M. G., Forwell, G. D. *J. Physiol.* 1956, **132**, 115.

tion to permit the formation of such a committee, and their protests are designed only to distract attention from the fact that their position is completely untenable scientifically.

New York. A. S. WIENER.

RESIDENTIAL CHARGES ALLOWABLE AS INCOME-TAX EXPENSES

SIR,—Because some inspectors of taxes refused to accept the decision in the appeal to the General Commissioners of Income Tax undertaken by the Medical Protection Society as a test case,[1] the Society made further representations to the Board of Inland Revenue on this subject.

The Board of Inland Revenue have now stated that they are prepared to agree that a married medical officer in the National Health Service, who is required by the terms of his appointment to live in the hospital in which he is serving, may be allowed a deduction under rule 7 of the ninth schedule to the Income Tax Act, 1952, for the full expense which he incurs for board and lodging in the hospital premises provided that :

(*a*) he is required to be on duty or call twenty-four hours a day and not to leave the premises except when a deputy is provided, and
(*b*) other accommodation is maintained outside the hospital for his wife where he normally resides when not on duty.

A similar deduction will be allowed where a married woman medical officer holds a post in the National Health Service on like conditions if she normally resides with her husband, when she is not on duty, in accommodation maintained outside the hospital.

The Board also states that appropriate instructions will be given to inspectors of taxes.

HERBERT CONSTABLE.
London, W.1. Deputy Secretary, Medical Protection Society.

A SIMPLE TILTING BED-FRAME

SIR,—While it is now generally accepted that raising the foot of the bed 9 inches is an essential part of the permanent aftercare of the post-thrombotic leg,[2] experience has shown that many patients tend to remove the unsightly wooden blocks the moment their legs are œdema-free—particularly women, who complain that they spoil the look of the bedroom. Messrs. Heals have now made for me a simple tilting frame which can be incorporated in virtually any existing bed.

1. See *Lancet*, 1958, i, 1393.
2. Rivlin, S., *Lancet*, 1958, i, 1363.

Clamped on the existing bed-frame, which is lowered $4\frac{1}{2}$ in., it takes over the duty of supporting the bedding, and since it is pivoted at its centre it is a simple matter to tilt it 9 in., resting the elevated foot-end on two "legs" which swing down (see figure).

This device has the additional merit that the bed sits four-square on the floor without strain, while when made up with its complement of bedding it looks completely normal when pivoted level in the daytime.

I am greatly indebted to Mr. A. E. Treleaven, of Messrs. Heals, for his care and attention to detail in evolving this device.

London, N.W.1. STANLEY RIVLIN.

ACUTE HÆMORRHAGIC NECROSIS OF PANCREAS DURING CORTICOSTEROID TREATMENT

SIR,—An example of pancreatic necrosis due to treatment with steroid hormones [1 2] was observed in our hospital.

A woman of 73 was admitted because of considerable weakness, loss of appetite, feverish states, and transient abdominal pain, independent of meals. There was distinct loss of weight, and a malignant tumour of the digestive system was suspected.

Her nutrition was poor and skin pale and yellow. Axillary glands palpable on the right side. In the abdomen the gall-bladder was slightly tender.

Hæmatological investigation indicated aplastic anæmia: Hb 30%, erythrocytes 1,790,000 per c.mm., colour-index 0·83, white cells 6500 per c.mm. (non-segmented 5%, segmented 40%, eosinophils 2%, lymphocytes 31%, monocytes 20%, plasma cells 2%). The bone-marrow was not very rich in cells, with an increased myeloblast count. Bleeding-time 1 min. 45 sec., coagulation-time 22 min., prothrombin level 72%, hæmatocrit 20%.

Fractional test-meal disclosed achlorhydria. X-ray examination of chest and digestive system was negative. Numerous gallstone shadows were visible.

Treatment included transfusions of fresh and stored blood, vitamin B_{12}, hepatic extracts, vitamin-B complex, vitamin C, and prednisone (30 mg. daily), with penicillin and then aureomycin. After $3\frac{1}{2}$ months in hospital she was discharged in good condition. At home, while having prednisone and vitamins, she got worse, and further transfusions were needed. After a time, during a hæmatological improvement, she became unexpectedly worse, with high fever, profuse perspiration, and vomiting. The blood picture deteriorated, and corticotrophin (A.C.T.H.) (100 mg. daily) was given. After a short improvement she got much worse and died of circulatory failure. No acute abdominal symptoms were present.

Unexpectedly, acute hæmorrhagic necrosis of the pancreas was discovered at necropsy. There were necrotic spots in the fat tissue under the mesentery, stones in the gallbladder, and abscesses in the right lung.

In the pancreatic parenchyma and in the interlobular fat tissue necrotic and hæmorrhagic spots were dispersed. In some hæmorrhagic spots, partly degenerated leucocytes were accumulated. The rest of the pancreatic parenchyma was fibrous, atrophic, and partly œdematous. Rare intralobular pancreatic ducts were dilated and empty. Atheroma was prominent in the pancreatic arteries.

Various factors have been thought to be responsible for acute hæmorrhagic necrosis of the pancreas during prolonged corticosteroid therapy: blood hyperlipæmia, deterioration of the endothelium of pancreatic ducts by steroids because of retention of secretion, allergic reactions to steroids, destruction of nucleoproteins of pancreatic cells by corticotrophin, primary pathological process in pancreatic vessels (periarteritis nodosa, atheroma).

In experimental conditions acute hæmorrhagic necrosis can follow ligature of pancreatic ducts and simultaneous

1. Carone, A. F., Liebow, A. A. *New Engl. J. Med.* 1957, **257**, 690.
2. Baar, H. S., Wolf, O. H. *Lancet*, 1957, i, 812.

administration of cortisone.[3 4] In these conditions the viscosity of pancreatic juice seems to change, and the ducts become occluded. The cause of necrosis in our patient could be numerous hæmorrhages, due to aplastic anæmia, and/or activation by steroids of a chronic pancreatitis associated with cholelithiasis. Atheroma in the pancreatic arteries could also play a part.

Central Clinical Hospital M.S.W., Warsaw.

STANISLAW DABROWSKI
JAN LOZINSKI
WLADYSLAW MIELNIK.

DEMONSTRATION OF MALIGNANT CELLS IN SPUTUM

SIR,—Many clinical laboratories are now called upon to employ various exfoliative cytological methods in the diagnosis of carcinoma, and the most common of these is probably the screening of sputa in cases of suspected bronchial carcinoma.

It is the custom in this area to examine three successive morning specimens of sputum from such cases. Selected mucoid portions of the sputum were smeared, fixed in Schaudinn's fluid, and stained by Mayer's hæmalum and eosin. After many unsuccessful attempts to demonstrate malignant cells in cases which subsequently were shown to have carcinoma, it became obvious that the content of malignant cells in the specimen would have to be high before such a method was likely to be successful. Some method of concentrating the content of malignant cells was obviously necessary, and the enzymic digest method of Rawlins,[5] using buffered pancreatin, was tested.

The sputum is received in a sterile universal container and to this is added an equal volume of buffered pancreatin solution (Oxo Ltd., Medical Dept.). It is then incubated in the oven at 37° C. After approximately 90 minutes the specimen is centrifuged and two smears of the deposit are then fixed in Schaudinn's fluid and stained with hæmalum and eosin.

Our first application of the method was strikingly successful. The first two specimens from the patient had been reported negative by the direct method. The third specimen also appeared to be negative but after applying the digest method we were surprised to find malignant cells to be present in numbers. This confirmed our suspicion that the specimen may be abundantly contaminated by malignant cells and yet random sampling fail to yield a positive result. We have since noted on several occasions scanty malignant cells by the digest and concentration method which, it seems fair to assume, would have been missed by the direct method. We have not sufficient figures to permit of any statistical analysis of the performance of the method but are convinced of the advantages of the concentration of the malignant cells which it achieves without apparently interfering with the staining affinities of the cells.

Pathology Department, Ballochmyle Hospital, Mauchline, Ayrshire.

J. STEWART
P. J. NORRIS.

FALLS FROM A HIGH CHAIR

SIR,—The World Health Organisation [6] has emphasised the importance of accidents as a major cause of mortality and morbidity in childhood. With this in view, we should like to make known the results of an investigation into falls from a high chair.

In carrying out our investigation, data were obtained in two ways:

(1) Mothers bringing their children to our casualty department were interviewed and the following results were obtained:

No. of children	618
No. of children who used high chairs	431 (69·7%)
No. of accidents	52 (12·1%)

Thus, on the basis of our sample, almost 70% of infants are reared in a high chair, and, of these, nearly 1 in every 8 has one or more falls from it. The types of injuries sustained were mainly minor—bruises and cuts. However, there were cases of fracture (nose, skull) and loss of consciousness with or without concussion. Even the use of straps, though greatly decreasing the incidence, did not prevent falls entirely.

(2) All emergency admissions to this hospital, under the age of 2 years, in the years 1954–56, were sorted, with the following results:

	No. of admissions	*Due to falls from high chair*
1954	251	0
1955	330	0
1956	234	2

1 of the 2 cases noted sustained a right parietal fracture, the other, severe laceration of the tongue.

The following conclusions may be drawn:

(1) Approximately 1 in every 8 children using a high chair has one or more falls from it. The injury sustained is usually not sufficiently severe to warrant admission to hospital.

(2) The frequency of accidents and the possibility of serious injury argue against the use of high chairs or, at least, for changes in their design.

Westminster Children's Hospital, London, S.W.1.

M. GLASSER.

INFLUENZAL ENCEPHALITIS

SIR,—In previous letters [1 2] with Dr. R. A. Goodbody, I drew attention to the clinical and pathological features of influenzal encephalitis. Subsequently [3] we suggested that this condition has an allergic basis and that modern antiallergic therapy, if instituted early, may influence the outcome. The pathological appearances prompted us to urge the use of cortisone or its derivatives as a trial in conjunction with suitable antibiotic cover. Previously McConkey and Daws [4] had independently used a steroid with success.

In the last influenzal epidemic I had an opportunity of testing this hypothesis further, and I feel that the successful outcome justifies recording the case.

A roadman, aged 35, was admitted to Lymington Hospital, Hants, on Feb. 22, 1959, with bilateral bronchopneumonia. He had fallen ill six days previously with typical influenza, but he had insisted upon continuing at his work for three days because he had a large family of a wife and six children to support.

On examination, on Feb. 22, he was found to be semi-conscious and slightly cyanosed. Pulse-rate 126, good volume. Signs of bilateral bronchopneumonia with generalised emphysema. Slight œdema of both feet. Blood-pressure 150/90 mm. Hg. Cervical veins normal and liver not enlarged. Reflexes present and equal. Plantar responses flexor. No neck rigidity or Kernig's sign.

The urine contained no albumin or sugar. An X-ray of heart and lungs was reported as follows: "The lungs appear over-aerated with general bronchiolitis and bronchopneumonia at left base and right mid-zone". White cells 8300 per c.mm.; differential count normal. Blood-urea 45 mg. per 100 ml.

Despite intensive antibiotic therapy with penicillin and later streptomycin, with the addition of aminophylline, mersalyl, and digoxin, and an oxygen tent, he deteriorated, and on Feb. 26 death seemed inevitable. The blood-pressure was unchanged. The chest had cleared considerably clinically, and he had remained afebrile, but if he was taken out of the oxygen tent, he became deeply cyanosed. The retinæ were normal, but there was by then marked evidence of bilateral

3. Stumpf, M. M., Wilens, A. W., Somoza, C. *J. Lab. Invest.* 1956, **5**, 224.
4. Bencosme, A., Lazarus, S. *A.M.A. Arch. Path.* 1956, **62**, 285.
5. Rawlins, G. A. *J. clin. Path.* 1955, **8**, 114.
6. *Wld Hlth Org. tech. Rep. Ser.* 1957, **118**.

1. McGill, R. J., Goodbody, R. A. *Lancet*, 1958, i, 320.
2. Goodbody, R. A., McGill, R. J. *ibid.* 1958, ii, 156.
3. Goodbody, R. A., McGill, R. J. *Brit. med. J.* 1958, ii, 1294.
4. McConkey, B., Daws, R. A. *Lancet*, 1958, ii, 15.

pyramidal-tract involvement with accentuated knee and ankle jerks, bilateral ankle-clonus, and bilateral Babinski signs. He had made no complaint of headache at any time.

On Feb. 26 the cerebrospinal fluid was clear and colourless, and under normal pressure. It contained 4 lymphocytes and 63 red cells per c.mm. Total protein 35 mg. per 100 ml., sugar 84 mg. per 100 ml. No pathogenic bacteria were recovered.

The diagnosis of influenzal encephalitis was made, and treatment began on Feb. 27 with chloramphenicol 500 mg. q.d.s., and prednisolone 20 mg. q.d.s.

From being in extremis (his relatives had been warned of the approaching end) he gradually improved, and by March 2 he was more conscious. The plantar responses were then flexor. Next day he regained consciousness. Improvement thereafter was maintained. Increase in all reflexes persisted, with ankle-clonus, until March 6. An X-ray of heart and lungs on March 9, showed complete clearing of the bronchopneumonia. He was discharged from hospital on March 23, completely recovered.

Agglutinations against the viruses of influenza were as follows:

	Influenza A	*B*	*C*
March 3	160	<10	10
„ 23	160		10
April 10	80	<10	10

These results indicate a recent influenza-A infection.

This man had influenza A followed by bronchopneumonia, evident clinically and radiologically, and confirmed subsequently by virus-agglutination tests.

Similarly, he undoubtedly had clinical encephalitis, this being shown repeatedly. The cerebrospinal fluid may be quite normal in this syndrome.[1 5] He would probably have died without prednisolone.

Lymington Hospital, Hants. R. J. McGILL.

Medicine and the Law

Death after Boxing Blow

AN inquest was held at Romford on Dec. 7 into the death of a young R.A.F. man who had received a heavy blow on the head during a boxing match. We are indebted to Dr. W. W. Walther, of Whipps Cross Hospital, for the following note.

While taking part in boxing trials, an 18-year-old R.A.F. boxer of considerable experience received a heavy blow on the forehead which brought him down on one knee, but from which he soon recovered. He did not resume, as it was the end of the bout, and he appeared to be perfectly fit.

About one hour later, he complained of headache and nausea and became unconscious. On removal to hospital, decompression was carried out, but the patient did not improve and he was transferred to a neurosurgical unit where a flap of skull was turned down and blood-clot evacuated. The patient died approximately three weeks after the injury. At postmortem examination he was found to have a black eye on the left side and various operation incisions of the scalp. Some old hæmorrhage stained the left cerebral hemisphere and there was a considerable laceration of the temporal lobe. The brain substance was considerably swollen. Other findings included early bronchopneumonia in both lungs (a tracheotomy had been done), and a small pulmonary embolus in the left lung. The coroner recorded a verdict of accidental death due to laceration of the brain.

A Nigerian middleweight was knocked out in a fight at Wolverhampton last week.[6] He was taken to hospital and underwent an emergency operation on Friday. He died the same night.

5. Crawford, T. *J. clin. Path.* 1954, **7**, 1.
6. *Birmingham Post*, Dec. 14.

Parliament

A Social Research Council?

IN the course of his opening speech in the debate in the House of Lords on Dec. 9 on the increasing role of science in the service of society, Lord TAYLOR said that medicine was the oldest example of Government intervention in science, for the foundation of the regius professorship in physic just antedated Government interest in astronomy for navigational purposes. He believed the Medical Research Council to be a model of Government intervention in the sciences. The membership was, and always had been, first-class, and the return which we got as a nation—indeed, which the world got—in terms of human health and happiness for the relatively microscopic expense of £3½ million a year could be reckoned in hundreds of millions of pounds.

The Council ran the great National Institute for Medical Research at Mill Hill; it ran 65 research units and groups, many of international repute; and it ran the excellent Public Health Laboratory Service. But it ran much else besides. It was not afraid to have two or three groups of people working together on similar lines, even if they overlapped, because it had a policy of backing good men, whatever their field of interest. It was not afraid to have part-time directors and workers on its staff, for it recognised that some people did their best work with a multiplicity of interests. It was one of the least rigid of Government organisations. But, inevitably, the Council had a large number of specialised research committees, and the volume of paper which came to the Council itself for final decision was enormous. Was this really inevitable? He also thought that the Council was a little doubtful about its constitutional power to delegate authority. As a result meetings of the Council, which should be a forum for general discussion on broad scientific medical policy, too often tended to be cluttered with detail.

The Council's positive decisions were almost always right. They almost never backed a loser, but they did, he believed, sometimes fail to back winners. There were three reasons for this. Most members of Government scientific councils were senior people, and it was an occupational risk of senior scientists to develop a certain intellectual negativism. The second difficulty which the Council ran into was the opposite side of one of its great virtues. As a broad principle, it backed good men, whatever their ideas and fields of work. It did not say, "Here is our problem which must be tackled, and we will find the men to do it". The latter method of tackling a problem was admittedly much more risky and much more costly. But it was the way in which most of our atomic research was being done. And it was beginning to be used in medicine in the United States. Three projects which Lord Taylor suggested might be tackled in this way were the biochemistry of schizophrenia, a vaccine for neoplastic tissue, and a biochemical agent to cure high blood-pressure.

The third difficulty which arose with the Medical Research Council was in relation to the universities. It was always possible to get grants of £3000–£10,000 for small-scale research projects lasting from one to three years. The difficulty arose for young research-workers at the end of three years. There was a great shortage of endowed readerships and research professorships with the necessary laboratory and other staffs. Universities were even reluctant to accept donations which would enable them to endow readerships or professorships unless at the same time they saw where the money for the professor's staff was going to come from. Thus every year good research-workers were lost to clinical medicine. Here, too, Lord Taylor thought, the Medical Research Council could help, provided it had the money to do so. The other side of this difficulty was the unwillingness of the universities to recognise Government research units and organisations as approved places for study for higher degrees. He understood that the Medical Research Council was toying with the idea of a research hospital, somewhat on the lines of the great Bethesda hospitals

in the United States. This had much to commend it, but he wondered whether it would not be better to have several hospitals, each with a specialised research unit in a single subject, rather than try to have the whole lot together in a single place.

Preventive psychiatry was one of the most important growing points in all science, for here we sought to find out by scientific method what kind of society would do most to create a healthy mind. We were already finding out that it was not a purely materialistic society. Too much material wealth was bad for men's minds, just as too much material poverty was bad for men's bodies. Science could be applied to help solve the problems of society, and he believed that the time had come to establish a Social Science Research Council alongside the other great research councils. He realised that social research was still very immature. It had only just learnt to measure—indeed, sometimes it was a little too preoccupied with measuring. Society presented so many problems for research that it was easy to waste time studying irrelevancies. The need was for long-term social studies—not merely analytical, but also constructive—stretching out into what might be called social engineering and social architecture. As urgent problems he proposed the best size of organisations for social efficiency, whether they were hospitals, factories, towns, or even research councils; conurbations; communications, whether by word, sight, or movement; social morality; and relations and understandings between the great groups of society, the nations. For success, social science needed the stern discipline of natural science; but it also needed courage and a sense of adventure—a willingness to set targets high and to take risks.

During the debate several Noble Lords returned to the suggestion of a Social Research Council. The Bishop of CARLISLE thought that there was a tremendous need for the kind of research that such a body could support—research into the art of living fully and happily in a society where material prosperity prevailed. We used to know what the problems of poverty were, but we were only beginning to glimpse the problems of continuous prosperity.

Lord ADRIAN, too, was concerned to support Lord Taylor's plea for more encouragement for social science. But we could scarcely blame the Government for its neglect. We must blame ourselves, and to some extent the subject. In sociology there was a great lack of senior men for teaching and research, and there was a lack of posts which they ought to fill. We were far behind the United States in the help we gave, and there was a danger that the good students would go off into other fields if the subject was allowed to remain as it is now. Sociology was still trying to find its feet, and it had an uphill fight because of the nature of its material. The natural scientist was on a much easier wicket. He studied dependable things, like sugar molecules or electron orbits: he could do experiments, and he had controls to keep him on the right line, to prevent him from being swayed by his prejudices and his emotions. The social scientist had to study undependable things like live human beings, all modified by their upbringings, in varied surroundings, and exposed to constantly changing conditions which were never going to recur, so that one could not easily check the results. Thus sociology had a long way to go before it would reach the status of real scientific impartiality, but it was high time that we gave it a better chance of doing so. We had urgent reasons for wanting to know more about the way people were likely to behave in a civilised society.

He agreed that the most important thing was provision for more permanent endowment of chairs and senior research posts in institutes of sociology. He was not quite sure that the time was ripe for a Social Science Research Council on the lines of the Medical Research Council. Councils and committees rarely initiated good lines of research, though, if research had begun, they could help a great deal to keep it going. But it was clear that there was a strong case for a preliminary survey of the need for a council, and for deciding the fields it might be expected to cover.

Speaking at the end of the debate Lord HAILSHAM said that in 1946 a proposal for a Social Research Council, similar to that which Lord Taylor had put forward, was investigated at the request of the then Government, and rejected. He did not necessarily say that the decision of 1946 must stand for all time, but he would say that it did not follow that, because the social sciences needed encouragement, a council was the right organisation to do it. For almost any immature science the university was the place where the work ought to start, and the individual project was the way of starting it.

Welfare of Office Workers

On Dec. 11 Mr. RICHARD MARSH introduced, as a private member's measure the Offices Bill to make further provision for health, welfare, and safety in offices. Every day, he said, thousands of people went to work in offices which were not only uncomfortable but often dangerous to health, life, and limb, where the lavatories were inadequate, where there were no lavatories, where there were no washing facilities. Not all offices were bad, but there were enough bad offices to make it essential to improve conditions. The Gowers report was published in 1949, but nothing had been done about it. Now it was suggested that the growth of new office building and the passage of time had rendered it obsolete. There were no national records of how many offices had no lavatory accommodation, no figures to show how many offices had inadequate temperature control, and how many were overcrowded. But a survey last year in Liverpool had shown that only 176 offices out of 269 had wash-basins in the offices, and 109 of those had no hot water. Only 38% had drinking water available. In 16 firms there was no water-supply at all. There was no reason to assume that conditions were better anywhere else. Nor was overcrowding prevented by building a big office. Whether an office was overcrowded was determined by the number of people who were crammed into it. There could be as much overcrowding in a new office as in an old one.

Mr. E. C. REDHEAD, who seconded the Bill, said that this was the sixteenth Bill within 36 years which had been brought before the House. But for offices there were still no enforceable standards of space, ventilation, lighting, or water-supply. Contrary to a common belief, public-health inspectors had no power to inspect offices and could intervene only if their attention was drawn to some specific gross insanitary defect.

Mr. DENNIS VOSPER, joint under-secretary of State for the Home Department, said that the Gowers Committee had reported at a time when restrictions were inevitable in many aspects of our life. Since then there had been enormous expansion in office building. One difficulty in dealing with the problem was the lack of information. The number of offices which would fall to be dealt with under the Bill must be at least 1 million. The true extent and nature of the deficiencies were not known. Health and safety were the primary conditions in factory legislation, but in offices welfare predominated, and it was arguable whether legislation would be effective. It might well be that the only practical effect would be to place a considerable burden on many small employers. If the provisions were strictly and immediately enforced, many small employers would be put out of business. Capital investment which would be better employed in urban redevelopment and in providing new office accommodation would be diverted to what would be a mere temporary expedient. Enforcement would present enormous difficulties and an office inspectorate would have to be established and suitably instructed in its task. It would inevitably be a long time before local inspection and follow-up action began to make their contribution towards the solution of what might well be a diminishing problem. If it took 400 factory inspectors to inspect a quarter of a million factories once every four years, the House could calculate the size of the inspectorate necessary to inspect over 1 million offices.

The Government believed that a positive approach to the problem was the redevelopment of the central areas of cities and towns in which most office accommodation was situated, and this was proceeding. The Minister of Works estimated

that about £45 million was spent in office building in Great Britain in 1955 and that this figure would rise to about £70 million in the current year. Given another ten years, he believed that there would be few offices which did not measure up to the spirit of the Gowers Committee's recommendations. To codify standards at this stage might retard expansion, for the formal minimum of the Gowers standards might well become the maximum. The Government felt that arguments for introducing legislation were not so strong as some years ago.

In his opinion it would be difficult for this Bill to be amended sufficiently within the scope of Private Members' time. The Government did not wish to rest their apprehensions about the Bill merely on defects. They were confident that its purpose could be achieved on the basis of competition, fair dealing, and enlightened self-interest, without the need for legislation. It was nearly eleven years since the Gowers Committee completed its work. There was little specific evidence about the conditions in offices in general, and the Government felt that further up-to-date information was needed and they proposed therefore to ask selected local authorities to report on the situation as they see it today. The Government felt that this Bill should not proceed and that the House should await the results of the inquiry.

But many members seemed to regard a meeting of selected local authorities as inadequate, and Mr. W. E. PADLEY asked "Will it bankrupt British employers to provide one lavatory for each fifteen or twenty-five persons of either sex? Will it really bankrupt Britain in the 1950s, or ruin a large number of employers, if proper washing facilities with hot and cold running water have to be provided?" On a division the second reading of the Bill was carried by 129 votes to 76.

New Bills

On Dec. 9 in the House of Lords, the Lord Chancellor introduced the Indecency with Children Bill which makes further provision for the punishment of indecent conduct towards young children and increases the maximum sentence of imprisonment under the Sexual Offences Act 1956—for certain existing offences against young girls.

The Lord Privy Seal and Minister for Science introduced the Public Health Laboratory Bill to establish a Public Health Laboratory Service Board to exercise certain functions in the administration of the bacteriological service provided by the Minister of Health under the National Health Service Act, 1946.

QUESTION TIME

Drug Addiction

In answer to several questions, Mr. DEREK WALKER-SMITH, the Minister of Health, said that one of the recommendations in the interim report of the Interdepartmental Committee on Drug Addiction, which would be published shortly, was that, in general, any drug or pharmaceutical preparation which had an action on the central nervous system and was liable to produce physical or psychological deterioration should be confined to supply on prescription. The committee further recommended that an independent expert body should advise which substances should be so controlled. As an interim and urgent measure, the Home Secretary was asking the Poisons Board to advise him which substances should be limited to supply on prescription under the Pharmacy and Poisons Act, 1933.

Group Practice Loans

The total number of loans for group practices so far approved is 180, amounting to about £900,000. The number of loans approved in 1959–60 to date is 26, to the value of £209,000.

Health Centres

So far 10 new health centres have been provided under the National Health Service Act. 92 general practitioners are working in these centres. 4 more centres are being provided, and 4 further centres have been approved.

Obituary

ERNEST FAVENC CHIN

M.B. Sydney, F.R.C.S.

Mr. Chin, whose death in a motor accident on Dec. 5 we announced last week, was appointed director of thoracic surgery to the Wessex region in 1951, when it was still the Western area of the South West Metropolitan Regional Hospital Board. In seven years, from a small sanatorium block and some old isolation wards, he created one of the most up-to-date thoracic surgical centres in the country.

He was born in 1913 in Sydney and qualified from the university there in 1940. He joined the Royal Australian Navy and spent the next five years at sea, sometimes on North Sea convoys to Russia. After the war he came to this country to continue his surgical training, and he took the F.R.C.S. in 1948. The years he spent at Harefield, working with Mr. Holmes Sellors (whose personal appreciation we published last week), were especially important for his development. Before taking up his appointment at Southampton he worked as surgeon to the thoracic unit at Harefield Hospital and as thoracic surgeon to Preston Hall, Aylesford, and King George V Sanatorium, Godalming.

W. S., who came to know Mr. Chin in the early days of the Southampton unit, recalls:

"Paul Chin had clear ideas of how a unit should be formed, how it should work, and what it should achieve. His excitement and impatience were unconcealed. He had little if any financial ambition, but supreme self-confidence in his ability to build a surgical centre which would be efficient and successful. He spurned false modesty and spoke as frankly about his capabilities as his limitations. He often spoke of his gratitude to Holmes Sellors for his early training, yet he held strong views that a young surgeon should not follow a single master, but should glean and try to perfect the best of all technicians. Chin's ideas centred around teamwork and he expected his colleagues to show the obsessional industry and self-sacrifice that came naturally to himself. If they failed, he would be intolerant. He was fascinated by the concept of a perfect surgical and medical partnership. It was this ambition and purpose which made it a remembered joy to work as a physician with him."

W. M. M., who was latterly the medical partner of the Southampton team, writes:

"A man of tremendous stamina, Paul Chin spared no-one, least of all himself, in his determination to ensure success. All hours, day and night, all days of the week, might see him in the middle of his work. The creation of the unit was the paramount purpose of his life; his family had to come second, and during these difficult formative years his wife, with some sacrifice, gave him strength and support in his resolve. It was only in recent months that he admitted his intention to take more leisure and spend more time with his family in the lovely surroundings of their cottage at Nether Wallop. During these very full days he still kept a clear eye on the future. He knew in which direction he had to go, and with the power of his convictions he would accept no barrier, no block would hold him back. With almost ruthless resolve and singleness of purpose he would achieve his end, not for any self-glorification but for the growth and greatness of his unit and the part it was to play. He had no use for half-truths or humbug. He was forthright and outspoken in his views. He would thrust and thrust hard. At times abrupt in manner, he could hurt, and some would take offence. Others misread conceit into the shield of his shy reserve.

"The earlier years of his work in Southampton coincided with the peak period in the operative treatment of pulmonary tuberculosis. In no branch did he demonstrate better his complete mastery of lung surgery. It was not confined to the narrow limits of operative technique but began with a shrewd assessment of the patient and his disease, and continued

through the postoperative days into the years by a personal follow-up. His œsophageal work was governed by a constant fascination with physiological principles. In diaphragmatic and chest-wall disease he tried to fathom the developmental origins of malformations. With recognised authority he planned his operations, no wires, no tricks, simple and effective, and many of his patients were spared deformity. Of late he had entered with characteristic enthusiasm the field of cardiac surgery, and the remarkable success of his unit is a witness of his brilliance. A few moments before he left on his last journey home he was discussing with some of his colleagues what he called ' phase 3 ' in the development of his unit. There was to be no sitting back or placid contentment, but still further progress in thoracic surgery.

"He had a simple faith, undemonstrative and sincere. Towards the end of one of his cardiac operations, contrary to his usual practice and for no conscious reason, he reopened the atrium and out flushed a large clot which certainly would have proved fatal. He later remarked with true humility that success was not in his hands alone.

"All men may leave a mark on their departing, but some are weak and others seize not opportunity. With E. F. C., his thoracic unit is a fair measure of his stature and a living memorial to a great surgeon."

Mr. Chin married in 1942. He leaves a widow and three sons.

HUGH WILKES MACINTYRE

M.B. Lond., M.R.C.P.E., D.C.H., D.Path.

Dr. Hugh Macintyre, pathologist to Hertford County Hospital, died at his home at Ware on Nov. 12 at the age of 38.

He was educated at Liverpool College, Epsom College, and University College Hospital, London. He qualified in 1946 and held house-appointments at University College Hospital and at the Kent and Sussex Hospital, Tunbridge Wells. After two years of National Service in the R.A.F. he took the D.C.H. and became junior registrar in pathology at the Central Laboratory, Liverpool. Later he was appointed registrar in pathology at St. Mary Abbot's Hospital, London. During this time he took the Edinburgh M.R.C.P. with hæmatology as special subject. After a year with a Fulbright travelling fellowship at Meadowbrook Hospital, New York, and Cornell University, he became a senior registrar in clinical pathology at the Withington Hospital and Royal Infirmary in Manchester. He was appointed consultant pathologist to the Hertford group of hospitals in 1956. He had lately been elected secretary to the group medical advisory committee and a council member of the East Saxon branch of the Association of Clinical Pathologists.

A. G. S., in whose laboratory Macintyre worked as a trainee, writes:

"Hugh Macintyre came out of the R.A.F. determined to make pathology his career, and when I first met him he was a shy, retiring man who realised the obstacles to becoming a consultant in the National Health Service only too well. But he was prepared to work and make sacrifices to achieve his aim, and he obtained his consultant appointment at the age of 34. He was never known to be cross or upset by the most unreasonable demands of his colleagues, junior or senior, and his disposition was to live in peace and play his part in the development of clinical pathology. He had a very inquiring mind, and never failed to ask advice and invite criticism whenever he came across a rather more ticklish problem. His quiet friendliness will be missed by all who knew him."

W. D. L. writes:

"Hugh Macintyre came to Hertford, and by quiet, persistent persuasion proceeded to improve enormously the laboratory and pathology service. He was absorbed in his work, and that and his home and family, with an occasional round of golf, were his interests. Those of us who knew him well came to admire and prize his calm unruffled approach to his work and his thoroughness and neatness in doing it."

Dr. Macintyre leaves a widow and an infant daughter.

Notes and News

NUFFIELD FOUNDATION

THE grants made by this Foundation in 1958–59 for the first time exceeded £1 million.[1] In all £1,378,000 was distributed on scientific, medical, and social projects and on fellowships. Since the Foundation was created in 1943, it has disbursed nearly £9 million. Grants for medical research last year included:

University of Edinburgh.—£50,000 for research on the fibroblast in the departments of zoology and animal genetics under Prof. Michael Swann and Prof. C. H. Waddington.

Institute of Urology, University of London.—£25,000 over five years to finance the metabolic unit.

Institute of Psychiatry, University of London.—£17,000 over five years for an investigation into mental disease in general medical practice by Dr. Michael Shepherd. About 30 general practitioners are taking part in this study of the distribution of mental illness in the community and the proper scope of the general practitioner's work in psychiatry.

Ministry of Health, Kenya.—£50,000 for the establishment at Kitui of a " better living " institute, a combined health and agriculture centre for 60 people, where farmers and housewives will be instructed in the principles of good food production, home hygiene, and nutrition.

CHAIRS AND SQUARES

THE Parliamentary and Scientific Committee held a conversazione at Burlington House on Dec. 9. Among the exhibits was a study of posture in relation to efficiency and comfort—a subject so popular and important that the exhibit had five eager sponsors: the Anatomical Society, the British Psychological Society, the Ergonomics Research Society, the Physiological Society, and the Furniture Development Council. In one demonstration a " victim " sat on a chair of adjustable height and strove to control by foot-pedals the movements of a pattern in front of him. His success or confusion was recorded and related to chair height. Slight deviations from the optimum height made things very difficult for the performer. Also used in these investigations were the back-pressure recording chair and the intriguing wriggle-meter.

The Pharmaceutical Society of Great Britain's exhibit described the making of the British poliomyelitis vaccine and was constructed in collaboration with the three manufacturers. It made plain how long it took to complete the process and how stringent were the safety tests. Visitors interested in an earlier phase of man's activity could examine (but perhaps not eat) some specimens of foods lately found in the tombs of ancient Jericho by excavators from the British School of Archæology in Jerusalem. These bronze-age titbits of 4000 years ago are thought to include sheep or goat meat and bread made from millet. More readily identified was the world's oldest tin of food, made in Bermondsey in 1823, and no doubt just like the ones the printers opened at lunch-time when they were working on the first issue of *The Lancet*.

Much activity centred around Daedalus, a slow-speed computer designed to play the game of " completing the squares ". By means of 168 cold-cathode tubes and 1 thermionic tube Daedalus played a coldly calculating game, trapping all comers in his logical circuits. When he conceded first move, as he sportingly did very often, he was more vulnerable and was even seen to lose on occasion and to emit a groan of despondency. Daedalus was provided by Ericsson Telephones Ltd.

FOOD ENRICHMENT IN SOUTH AFRICA

THE National Nutrition Research Institute of South Africa has just completed a thorough study of the possibilities of reducing the widespread signs of protein deficiency by the use of fish flour for the enrichment of bread.[2] Large quantities of fish, mostly pilchards and massbankers, are landed at harbours

1. 14th report of the Nuffield Foundation, Nuffield Lodge, Regent's Park, London, N.W.1.
2. The National Research Institute of South Africa: a Study of Principles of Food Enrichment and Their Application to Food Policy in South Africa. 1959. Obtainable from the Council of Scientific and Industrial Research, P.O. Box 395, Pretoria.

which are remote from marketing centres. From these fish, it is possible to prepare commercially a protein-rich flour which could be used to enrich bread up to a level of 4%. This would not appreciably alter the taste, appearance, or physical characteristics of the loaf. Thorough tests in the laboratory have shown that the protein in this flour is of good biological value for rats, and no evidence of the presence of any toxic factor has been found. The enrichment could be made at a cost which is low in relation to the added nutritive value.

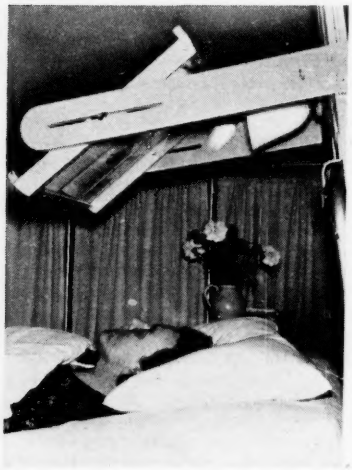
Nevertheless, the report does not recommend this enrichment. Protein malnutrition is widespread only amongst the Bantu children between the ages of 6 months and 5 years. Sales of bread are confined largely to the cities and country towns. The scheme would be ineffective in reaching that section of the population who are in need of the extra protein. A large proportion of the enriched bread would be consumed by persons whose diet was already adequate.

The report ends with recommendations for further study of possible methods of getting what is obviously a valuable food to the non-European population living in rural areas. The health of the children would probably be greatly benefited if suitable means for distributing this new food could be found.

The workers responsible for the laboratory side of this report are to be congratulated on having done a thorough job. They have produced abundant evidence that the nutritive value of fish flour is high. The usefulness of their work will remain negligible until the complementary advances in the social-science aspects of the problem have been made.

A BOOK-HOLDER FOR RECUMBENT PATIENTS

Dr. DUDLEY HART has sent us this photograph of a book-holder which is in use at the Westminster Hospital, London, S.W.1.



"We do not claim," he says, "that the book-holder is original; doubtless many variations are in general use. This one was invented and made by one of our hospital carpenters, Mr. H. E. Tabor, for a few shillings. Consisting essentially of a mobile easily manœuvred window on which any reading matter—book, newspaper, or magazine—can rest, it fits on to the end of the bed of any patient who has to be nursed flat on his back. The pages can be turned easily by the patient, who reaches up without altering his position in bed or moving his back. We have found it particularly useful in cases of prolapsed intervertebral disc."

University of Birmingham

The title of professor of cardiac surgery has been conferred on Mr. A. L. d'Abreu. Sir Arthur Thomson has been appointed senior fellow in medical history, Dr. A. P. D. Thomson acting director of the department of anatomy, and Mr. J. A. Williams lecturer in surgery.

Glasgow Royal Mental Hospital

On Dec. 11 Sir David Henderson opened a £100,000 extension to this hospital. It is intended for women patients and includes 30 single rooms and 8 six-bedded dormitories as well as common-rooms.

Royal College of Physicians of London

On Tuesday, Jan. 12, Dr. F. Ray Bettley will give the Watson Smith lecture. He will speak on some effects of soap on the skin. On Thursday, Jan. 14, Prof. J. W. Crofton will give the Marc Daniels lecture. The title of his lecture will be Tuberculosis Undefeated. On Tuesday and Thursday, Jan. 19 and 21, Dr. John Badenoch will give the Goulstonian lectures. He will speak on steatorrhœa in the adult. All the lectures will be given at 5 P.M. at the college, Pall Mall East, S.W.1.

Royal College of Physicians of Edinburgh

The office-bearers of the college for the coming year are:

President, Dr. A. Rae Gilchrist; vice-president, Dr. J. D. S. Cameron; members of council, Dr. I. G. W. Hill, Dr. J. Halliday Croom, Dr. T. Anderson, Dr. J. Laurie, Dr. H. J. S. Matthew; treasurer, Dr. J. Alastair Bruce; secretary and registrar, Dr. R. F. Robertson; hon. librarian, Dr. W. A. Alexander.

Royal Faculty of Physicians and Surgeons of Glasgow

At a meeting of the faculty on Dec. 7, with Mr. Arthur Jacobs, the president, in the chair, the following were admitted to the fellowship *qua* physician:

Mary Cherian, C. M. Fleming, Iris I. J. M. Gibson, Dorabji Minocher Joshi (Godrez), Robert Leishman, W. C. Love, Dante Mathuranayagam, G. Obiafo Onuaguluchi, Raj Kishore Saksena, D. A. L. Watt.

Royal College of Physicians of Ireland

On Dec. 4 the following were admitted to the licentiateship of the college:

Manfred Bayer, F. A. Caraher, G. M. Coleman, Rosaleen M. Devlin, Y. D. Docrat, J. E. Gordon, O. D. E. Herbert, P. R. Hodson-Fletcher, Anna Keane, Teet Meng Kwan, T. Nwogu Obonna, R. G. Magauran, Mairi F. McK. McPhail, F. F. Nally, Naoise O'Shea, R. H. Palmer, O. S. Samuel.

British Association of Otolaryngologists

The following have been elected officers of the association for 1960:

President, Mr. C. Gill-Carey; immediate past president, Mr. L. Simson Hall; vice-president, Mr. R. R. Simpson; hon. treasurer, Mr. J. C. Hogg; hon. secretary, Mr. G. H. Bateman.

British Association of Plastic Surgeons

The following officers have been elected for 1960:

President: Mr. P. H. Jayes; immediate past president, Mr. Rainsford Mowlem; hon. treasurer, Mr. R. P. Osborne; hon. editor, Mr. A. B. Wallace; hon. secretary, Mr. John Watson; members of council, Mr. C. R. McLaughlin; Air Commodore G. H. Morley, Mr. E. W. Peet, Mr. Mortimer Shaw, Mr. J. S. Tough; overseas representative on council, Mr. W. Manchester (New Zealand).

Fourth International Goitre Conference

This conference, sponsored by the London Thyroid Club, the American Goiter Association, the Royal College of Physicians of London, and the Royal Society of Medicine, will be held at Church House, Westminster, S.W.1, from July 5 to 8. Abstracts of papers must be sent to the hon. secretary of the conference, Royal Society of Medicine, Dering Yard, 67c, New Bond Street, London, W.1, by Dec. 31.

Czechoslovakian Congress on Pædiatric Surgery

The first Czechoslovakian congress on pædiatric surgery will be held in Prague from May 23 to 25. Further particulars may be had from the congress office, 2, Ke Karlovu, Prague 2, Czechoslovakia.

The Imperial Cancer Research Fund gave a dinner for Prof. Geoffrey Hadfield on Dec. 8, when Sir Cecil Wakeley, the chairman, made a presentation to him on behalf of the council.

The Medical Protection Society have now moved to their new offices at 50, Hallam Street, London, W.1.

Appointments

BLACKBURN, JOHN, M.B. Leeds, D.P.M.: assistant psychiatrist (S.H.M.O.), St. Luke's Hospital, Middlesbrough.

PHILLIPS-MILES, DAVID, M.B., B.SC. Wales: M.O., Welsh Regional Hospital Board.

ROMANES, G. J., M.R.C.S., D.O.M.S.: part-time consultant ophthalmic surgeon, West Dorset group of hospitals.